Orthostatic Hypotension and Supine Hypertension in the Patient with Autonomic Failure
Lamarre-Cliche

Advances in Implantable Cardiac Devices
Palazollo, Singh
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As announced in the previous issue of the *Canadian Journal of General Internal Medicine* I have assumed the position of editor-in-chief for the journal. Building upon the excellent foundation that was created by the journal’s previous editors and editorial boards it is my goal to build up the journal’s profile both nationally and internationally. The *Canadian Journal of General Internal Medicine* began in 2006 as a means to improve communication amongst practising internists, internal medicine residents, health care planners, the Royal College and the CSIM. It was also intended to showcase GIM from across the country with respect to research productivity, educational activities, and the challenges and successes of clinical practice. These areas of focus will remain important for the *CJGIM*. We will not stray from the value that the journal brings to its readers with respect to continuing education and maintenance of professional competence.

What I hope to see added to the journal is an increased emphasis on the journal becoming an important medium for knowledge translation. One component of that agenda is to have the journal’s articles indexed in Pub Med. While this is not a simple task, it is achievable. The ground work has been started by virtue of the fact that the journal has had 8 years of uninterrupted publication, which is an essential requirement in consideration for indexing with Pub Med. The next step is to demonstrate the value of the articles published in *CJGIM*. One measure is how often these articles are cited in the peer reviewed literature. To increase the latter we will be looking for submissions to the journal that are high quality systematic reviews or original research articles evaluating the use of therapeutic or diagnostic interventions. Reporting on quality improvement projects will also be welcomed.

While we work towards getting the journal indexed, there are other achievements we would like to accomplish. The current pdf format for digitally storing the articles permits easy access to obtain the articles from the publisher’s web site but it does not enable Google Scholar searches to readily identify the articles. We will be creating a digital record of key words, authors’ names and the abstract contents that will be searchable by Google (and other search engines). An additional change that is on the horizon is the implementation of some new sections within the journal to highlight special areas of focus in research and education.

I look forward to working with the *CJGIM* Editorial Board and to serving the GIM community across the country in my new role as editor. I believe that this will be an exciting and transformational time.

**Reference**


Mitch Levine
En tant que rédacteur en chef, je suis convaincu que nous sommes à l’aube d’une enthousiasmante période de transformation.

**Reference**


**Mitch Levine**
Levemir® (insulin detemir) is indicated for the treatment of:

- type 1 diabetes mellitus in adults, adolescents and children 2 years and above
- type 2 diabetes mellitus in adults when insulin is required for the control of hyperglycemia
- type 2 diabetes mellitus in combination with oral anti-diabetic agents (OADs) in adults who are not in adequate metabolic control on OADs alone. For safety reasons, the use of insulin in combination with thiazolidinedione is not indicated
- adult patients with type 2 diabetes mellitus in combination with Victoza® (liraglutide) and metformin when Victoza® and metformin do not achieve adequate glycemic control

Levemir® is also recommended in combination with short- or rapid-acting mealtime insulin. Please consult the product monograph at http://novonordisk.ca/PDF_Files/our_products/Levemir/Levemir_PM_EN.pdf for important information on contraindications, warnings and precautions, adverse reactions, drug interactions and dosing. The product monograph is also available by calling us at 1 (800) 465-4334.

* Comparative clinical significance has not been established.
§ Injection Force=the force required to press the push-button on pens to inject insulin.
‡ Adapted from Hemmingsen H et al., 2011. This study compared the injection force of FlexTouch® with that of SoloStar® and KwikPen™. Injection force was measured at 3 constant push-button speeds delivering 80 units with SoloStar® and 60 units with KwikPen™. FlexTouch® was not tested at 3 speeds because the spring-loaded mechanism has no influence on the rate of insulin delivery. Instead, injection force was measured as the spring activation force at 80 units. The manufacturers’ recommended needles were used; NovoFine® (Novo Nordisk) 32-gauge tip extra thin wall (etw) 6 mm needle for FlexTouch® and BD (Franklin Lakes, NJ) MicroFine™ 31-gauge 5 mm needle for SoloStar® and KwikPen™. Only one needle of each type was used for all injection force tests to avoid variation in measured injection force caused by the flow stress of different needles.

† For the treatment of diabetes, where a prior trial of intermediate-acting insulin did not adequately control the glycemic profile without causing an episode of severe hypoglycemia or frequent episodes of hypoglycemia.

REFERENCES: 1. Levemir® Product Monograph, Novo Nordisk Canada Inc., September 2013. 2. Hemmingsen N, Nymeyer M, Hansen MR, Bushe D, Thomsen NB. A pre-filled insulin pen with a novel injection mechanism and a lower injection force than other pre-filled insulin pens (Mean Injection Forces: FlexTouch® 5.1N. At 4, 6 and 8 mm/s respectively: SoloStar® 13.5N, 19.1N and 26.9N; KwikPen™ 14.5N, 20.9N and 28.2N)
Acute Care SINS: Surgical Insights for the Non-surgeon
Chapter 8: Liver, Biliary System & Pancreatic SINS

Rachel G. Khadaroo MD PhD, James A. Shapiro MD PhD, Peter G. Brindley MD

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Summary
“Surgical Insights for the Non-surgeon,” or SINS, is composed of several short chapters intended to cover fundamental surgical knowledge for non-surgeons. The authors focus on surgical pearls, operative insights, and applied anatomy. In Chapter 8 of this series, the authors address the liver and portal veins; their discussion includes anatomy, surgeries, and transplantation.

Résumé
L’ouvrage « Surgical Insights for the Non-surgeon » ou SINS (aperçu de chirurgie pour le nonchirurgien) se compose de plusieurs courts chapitres conçus pour couvrir les connaissances fondamentales en matière de chirurgie chez ceux qui ne sont pas chirurgiens. Les auteurs se concentrent sur des « trésors de sagesse » tirés de leur expérience personnelle en chirurgie, certaines idées en matière d’interventions, et sur l’anatomie appliquée. Le chapitre 8 traite des veines hépatiques et de la veine porte; l’analyse porte notamment sur l’anatomie et sur les aspects liés à la chirurgie et à la transplantation.

Jaundice is a disease that your friends diagnose.
— William Osler, 1849–1919

Surgical maxim: Eat when you can, sleep when you can, and don’t ‘mess’ with the pancreas.

Anatomy
The gallbladder is the size and shape of a small pear (but considerably more “squishy”). It includes a fundus, body, infundibulum, and neck and straddles the undersurface of the liver. It is hollow and stores up to 100 millilitres (mL) of bile (during fasting), which is squeezed out following a meal. In the absence of pathology, bile is sterile, but bacteriuria increases with obstruction and advanced age (>60 years). Normally, bile travels from the gallbladder to the cystic duct (anatomic variants abound), which joins the common hepatic duct; from there, it drains into the common bile duct (CBD). When the gallbladder is removed, the bile duct takes over the functions of the gallbladder entire, and despite common myths, no dietary modifications are required!

The pancreas is about 12 to 15 centimetres (cm) long and is located in the retroperitoneum. The pancreas is both an endocrine organ (produces insulin, glucagon, somatin) and an exocrine organ (secretes trypsinogen, chymotrypsinogen,
elastase, carboxypeptidase, pancreatic lipase, amylase, and bicarbonate to neutralize stomach juices). These powerful enzymes are vital for breaking down food but can cause local damage and pain when they attack the person’s body instead, thus causing pancreatitis; this can cause havoc if there is uncontrolled internal leak after pancreatic surgery.

The pancreas is divided into the head (enclosed by the duodenum), the body (lying behind the base of the stomach), the tail (butting the spleen), and the uncinate (“hook-shaped”) process at the lower end of the head. The pancreatic neck is between the head and the body. The neck lies anterior to the portal vein. Anatomy becomes important when resection is contemplated.

Arterial blood supply to the pancreatic head comes from the pancreatico-duodenal arcade. This arcade comes both from the celiac (via the gastroduodenal and superior pancreatico-duodenal artery) and from the superior mesenteric artery (and its inferior pancreatico-duodenal branch). The tail, the body, and the neck also receive blood supply from the splenic artery’s pancreatic branches (arteria pancreatica magna [Latin] means “the big one supplying the pancreas”). Venous drainage for the pancreatic head is via the superior mesenteric vein (SMV). The body and the neck drain into the splenic vein. These, in turn, drain into the portal vein.

The pancreas drains exocrine enzymes via the major duct (of Wirsung) and an accessory duct (of Santorini). The main pancreatic duct joins the common bile duct just before the ampulla Vater, and both enter the second part of the duodenum (via the major duodenal papilla). The ampulla of Vater marks the transition from celiac blood supply to superior mesenteric artery supply, and the Sphincter of Oddi regulates its flow. The accessory pancreatic duct bypasses the ampulla Vater and enters the duodenum via the nearby minor duodenal papilla.

**Congenital Anomalies**

**Pancreas Divisum**
- Failure of dorsal and ventral pancreatic duct systems to join during embryogenesis
- Divided drainage: duct of Santorini and Vater papilla
- May contribute to pancreatitis
  - Controversial because the anomaly is common (about 10% of the population)

**Ectopic and Accessory Pancreas**
- Pancreatic tissue in the stomach wall, duodenum or ileum (Meckel diverticulum)
- Can cause bleeding, intussusception, obstruction, and, very rarely, malignancy

**Annular Pancreas**
- Where the entire pancreas encircles the duodenum
- Can be asymptomatic; but may lead to duodenal obstruction in infancy

**Calculous Biliary Disease**

**Biliary Colic**

**Pathogenesis**

Gallstones form and precipitate due to an imbalance in the substances that make up bile (the Small triangle).

- **Cholesterol**
- **Lecithin** (phospholipids)
- **Bile Salt** (sodium taurocholate)

**Two Main Types of Stones**
- Cholesterol gallstones
- Pigment gallstones
  - Calcium bilirubinate and calcium palmitate major component of pigment gallstones
  - Black or brown pigment stones
  - Black stones: more often with hemolytic states (e.g., hereditary spherocytosis, elliptocytosis)
  - Brown stones: earthy in texture; found in bile ducts; associated with infection

**Natural History of Gallstone Disease**
- Most are asymptomatic
  - 1–2% develop serious symptoms or complications
  - One-third will develop symptoms (but not serious)
  - Two-thirds remain symptom free (over 20 years)
- Mild biliary colic
  - Two-thirds will have further episodes in 1 year

**Clinical Presentation**
- Severe colicky epigastric or right upper quadrant (RUQ) pain
  - Lasts minutes to several hours
  - May radiate to back or to right shoulder
  - Typically aggravated by fatty foods
  - Associated with nausea and vomiting

**Diagnosis**
- Abdominal radiography
  - Not very useful: only 10–15% of stones are radiopaque
Ultrasonography (US)
- Procedure of choice: but a 5% false-negative rate

Cholescintigraphy (HIDA)
- Only very rarely needed (but is used to diagnose acalculous cholecystitis)
- Uses technetium-labelled analogues of iminodiacetic acid (hepatic IDA)
- Excreted into bile after injection
- Uptake by liver, gallbladder, CBD, duodenum should be seen after 1 hour
- Gallbladder fails to fill if acalculous cholecystitis present

Computed tomography
- Less sensitive than US for gallstones
- Effective only if concerns of gallbladder cancer exist

Management
- Elective cholecystectomy (i.e., remove the gall bladder) – usually done laparoscopically
- Laparoscopy cholecystectomy (also known as “lap chole”)
  - Fibreoptic scope inserted
  - Less invasive, but less direct visibility
  - Risks include a 5% conversion to an open surgery
- Very rare (1:500 – 1:1000) risk of CBD injury.
- Cholecystectomy by laparotomy
  - Surgical incision at the RUQ
  - More exposure, but more invasive

Acute Calculous Cholecystitis

Pathophysiology
- Inflamed gallbladder with associated gallstones
- Cystic duct obstructs gallbladder distends wall becomes inflamed and edematous
- 5–18% develop ischemia and necrosis
- 50% with uncomplicated acute cholecystitis have positive bile cultures
  - Therefore, cultures not useful

Clinical Presentation
- RUQ pain of longer duration than with biliary colic
- Tenderness and possible fullness in RUQ
- Murphy sign (inspiratory pain with deep RUQ palpation)
- May have nausea, vomiting, or increased temperature
- May have mild leukocytosis (<15) and mild elevation of liver function tests

Diagnosis
- US shows thickening (>4 mm), pericholecystic fluid, sonographic Murphy sign
  - Take time to review US scan
  - Stone may be impacted in Hartmann pouch or neck of gallbladder
- HIDA for atypical cases
  - Non-filling of gallbladder indicates obstructed cystic duct

Acute Acalculous Cholecystitis
- 5–10% of all acute cholecystitis; 1–2% of cholecystectomies
- More patients receive percutaneous drainage (see below) compared with surgery
- Higher morbidity and mortality rates compared with calculous cholecystitis
- Associated with severe illness; complications of other medical and surgical conditions
  - Intraepithelial mechanical ventilation; sepsis; burns; trauma; total parenteral nutrition (TPN); longstanding human immunodeficiency virus (HIV) infection
  - Therefore to be considered in moribund patients and patients in intensive care unit (ICU)
  - 50% incidence of gangrene, perforation, and empyema
  - Serious risk in patients with diabetes, who must be closely monitored

Clinical Presentation
- Similar to cholecystitis (but usually overall patients more sick)
- Diagnosis may be masked by other conditions
  - Patient often too sick to be able to provide full history (mechanical ventilator; multisystem failure)
  - Best clue is clinical suspicion (RUQ pain; comorbidities; US or HIDA findings)

Diagnosis
- US findings of cholecystitis, but in the absence of stones, patient being usually more sick
- HIDA – In more stable patients when the diagnosis is unclear; NOT recommended if patient too sick to be in
radiology for hours
  - False-positive rate 40% – morphine cholecintigraphy improves accuracy
  - CT – may be helpful
  • Look for gallbladder wall thickening, pericholecystic fluid, and potentially intramural gas
  • Also useful for other disorders that can be missed on US (e.g., pneumonia)

Management
• Cholecystectomy versus cholecystotomy
• Cholecystostomy tube
  - Percutaneous tube inserted into the gall bladder under ultrasound guidance
  - Can be life-saving!
  - Tube drainage may be preferable to surgery, given patient instability
  - BUT, gangrenous, emphysematous, or perforated gallbladder mandates urgent laparotomy

_Choledocholithiasis_
• Simply means “at least one gallstone in the common bile duct”
• “Primary” if stones originate in the biliary tract
• “Secondary” when stones migrate from gallbladder
• “Retained” if discovered within 2 years of cholecystectomy
• “Recurrent” if detected later than 2 years after cholecystectomy

Clinical Presentation
• 7–15% of patients undergoing cholecystectomy have common bile duct (CBD) stones
• 1–2% after lap chole without cholangiography
• Biliary colic, jaundice, clay-coloured stools, tea-coloured urine, with or without fever or chills

Diagnosis
• Elevated bilirubin, aspartate aminotransferase (AST) and alkaline phosphatase (ALP)
• US shows increased CBD diameter (which increases with age)
  - Normal size usually <5 millimetres (mm)
  - Add 1 mm for every 10 years over 50
  - More added when the patient has had a previous cholecystectomy
• Endoscopic ultrasonography (EUS) is the most sensitive test
  - Helps avoid the need for (and risks associated with) endoscopic retrograde cholangiopancreatography (ERCP)
  - However, it is invasive (requires a gastroscopy and specialized equipment and skills)
  - Magnetic resonance cholangiopancreatography (MRCP)
  - Not the ideal test for stones
  - Limited to centres that have MRI
  - Lengthy procedure
  • Endoscopic retrograde cholangiopancreatography (ERCP)
  - Diagnostic, but also therapeutic, for stone removal
  - Complications include bleeding, perforation, pancreatitis, and cholangitis (5%)

Treatment
• ERCP
• Cholecystectomy with common bile duct exploration
  - Risk of recurrent biliary symptoms if the gallbladder is not also removed

_Gallstone Ileus_
• Mechanical obstruction of the gastrointestinal (GI) tract from a large impacted gallstone
• Occurs through a biliary-enteric fistula between gallbladder and duodenum
• Usually follows an episode of severe cholecystitis
  - Gallbladder gangrene and perforation → erosion or necrosis into an adjacent viscus with an impacted gallstone
• Typically in patients over 70 years of age
• Rare cause of small bowel obstruction (SBO)
  - 1% of SBO
• The large gallstone usually obstructs in the narrowest part of the small bowel
  - Typically 2 feet proximal to the terminal ileum

Treatment
• Laparotomy

_Acute Cholangitis (Ascending Cholangitis)_
• Bacterial infection of the biliary ductal system
• May ascend from the junction of biliary tree and duodenum
• Ranges from mild to life-threatening

Pathophysiology
• Bacterial concentrations of the bile and biliary obstruction
• Commonly associated with common bile duct stones
• Secondary bacteremia as it worsens

Etiology
• Most common to least:
  - Choledocholithiasis (80%), benign strictures, biliary
enteric anastomotic strictures, cholangiocarcinoma; periampullary cancer

Clinical Presentation
- Charcot triad: fever, jaundice, and RUQ pain
- Reynold pentad: Charcot triad plus hypotension and mental obtundation

Diagnosis
- Clinical suspicion
- Lab work suggesting biliary obstruction - Leukocytosis, hyperbilirubinemia, elevated ALP and AST
- US, CT

Management
- Antibiotics (to cover enteric gram-negative bacteria)
- If hypotensive and septic, patient may require ICU admission and vasopressors
- Emergency biliary decompression (i.e., ERCP)
- Alternatively, percutaneous trans-hepatic cholangiographic (PTC) drainage
- Surgical decompression with T-tube insertion, only if ERCP or PTC both unavailable or fail
  - Surgery is last resort, given higher mortality compared with ERCP

Biliary Tubes and Drains
The T-tube is so called because its end is “T” shaped and is inserted into the CBD. It functions effectively as a drain (both internal and external) but may also facilitate imaging and instrumentation. It is usually only temporary. However, “the one that put it in decides when it comes out.” As such, the surgeon must be consulted before removing or clamping it. Usually, it needs to stay in for six weeks or so: until a solid track (fistula) is formed. (Refer to Figure 5 in Chapter 2: Tubes, Drains, and Ostomies.)

The cholecystostomy tube (or C-tube) is not so named because of its shape but because it drains the gall bladder via cholecystostomy. The C-tube is often placed through the liver parenchyma to the gallbladder but can also be placed directly, and hence even if these tubes “fall out” (a euphemism for “yanked out during transfer”), there are typically few cases of sepsis as a sequela. The surgeon must always be called to assess the time for removal! (Refer to Figure 6 in Chapter 2: Tubes, Drains, and Ostomies.)

Acute Pancreatitis
Nonbacterial inflammatory disease caused by activation, interstitial liberation, and autodigestion of the pancreas by its own enzymes

Etiology
- 40% gallstone
- 40% alcoholism
- Hypercalcemia, trauma, hyperlipidemia, genetic predisposition
- 15% or more remain idiopathic or miscellaneous

Pathophysiology of Acute and Chronic Pancreatitis
- Usually temporary obstruction of the pancreatic duct
- Injury results in acinar cell activation of digestive enzymes
- Two phases: systemic inflammatory response syndrome (SIRS) (release of proinflammatory mediators); followed by pancreatic necrosis
- With infection of pancreatic necrosis, patients become exceedingly sick!
- ICU support likely needed; early involvement required

Clinical Presentation
- Severe epigastric pain radiating through the back
- Nausea or vomiting
- Low-grade fever
- With or without profound dehydration, tachycardia, and postural hypotension
- Myocardial depression in severe pancreatitis (circulating factors)
- With or without pleural effusion (left-sided)
- Less than 5% experience a bluish discoloration (i.e., extremely rarely seen and not a useful indicator in a screening test)
  - In the flanks: Grey Turner sign
  - In the periumbilicus: Cullen sign
  - Indicates hemorrhagic pancreatitis with tracking of retroperitoneal blood

Diagnosis
- Serum amylase or lipase
- CT with contrast
- Cross-reactive protein (CRP) can predict severity (>150 mg/mL)
- US to determine if choledocholithiasis or gallstone pancreatitis
- Endoscopic US if high index of suspicion for a retained CBD stone
  - Also approximately 90% sensitivity

Ranson’s Criteria of Severity of Acute Pancreatitis, (with or without gallstones)
(Online aide-memoires and calculators are easily found and can be downloaded to smartphones)

Criteria upon initial presentation:
- Age >55
- White blood cell (WBC) >16,000/microlitre (µL)
- Blood glucose >200 milligrams per decilitre (mg/dL)
- Serum lactate dehydrogenase (LDH) >350 international units per litre (IU/L)
- AST >250 IU/dL

Criteria after 48 hours:
- Hematocrit fall of >10%
- Blood urea nitrogen (BUN) rise >8 mg/dL
- Serum Ca++ >8 mg/dL
- Arterial partial pressure of oxygen (PO2) <60 millimetres of mercury (mmHg)
- Base deficit >4 milliequivalents per litre (mEq/L)
- Estimated fluid sequestration >6 L

Mortality correlates with number of positive criteria:
- 0–2 = 2%
- 3 or 4 = 15%
- 5 or 6 = 40%
- 7 or 8 = 100%

Management
Conservative:
- Supportive care
  - IV fluids
  - Oxygen (O2)
  - NPO; with or without nasogastric (NG) tube
  - Nutrition
- Note: Enteral route with a nasojejunal (NJ) feeding tube highly desirable
- Reduces risk of bacterial translocation
  - Studies suggest that NG feeding adequate and can be used if NJ unobtainable
  - Important to provide enteral nutrition with high-protein, low-fat, and semi-elemental nutrition
- Reduces activation of pancreatic enzymes
- Bowel must be rested (i.e., NPO/NG/IV; referred to as “suck and drip”) if ileus or high-NG output
- Goal is maintenance of enteral nutrition (even if trickle-feeds to maintain gut mucosa)
- Reverse the cause
  - Eliminate principal insult (e.g., remove the gallstone; stop the medication)

Mild disease:
- Lap chole on the same admission with cholangiography or preoperative MRCP
- In approximately one-third of those that forgo cholecystectomy, recurrence within 8 weeks

Severe disease:
- Removal of stones in duct with endoscopic US or ERCP
- Elective lap chole once pancreatic necrosis or pseudocysts resolve
- Approximately 4 to 6 weeks
- Surgical pancreatic debridement by an experienced surgeon
- Especially if extensive infected pancreatic necrosis (see below “Pancreatic and peripancreatic necrosis” section)
- Ideally before irreversible sequelae
  - Portal venous or mesenteric venous thrombosis
  - Prophylactic antibiotics
    - Mild pancreatitis – antibiotics not needed
  - Increasingly understood as an inflammatory (not infectious) and retroperitoneal condition
    - Different if severe necrotizing pancreatitis
  - Broad-spectrum antibiotics that penetrate the pancreas
- Involvement of surgeon; stewardship with antibiotics

Gallstone Pancreatitis in Pregnant Patients
- First trimester
  - Best to wait and treat in second trimester (when less risk to fetus and mother)
- Second trimester
  - As above: safer to perform lap chole in second trimester compared with first trimester
  - Place in partial left lateral decubitus position to take pressure off inferior vena cava (IVC)
  - Move uterus and bowel away from RUQ
  - Administer heparin prophylaxis
  - Pneumatic compression stockings
  - Supra-umbilical position
  - Avoid pneumoperitoneum (keep pressures <10–12 mm Hg)
- Third trimester
  - Advisable to wait till after delivery
  - Peripartum abdomen too “crowded” for routine lap chole

Pancreatitis: Prognosis
- After day 2, CRP >150 mg/mp predicts severe pancreatitis and pancreatic necrosis
- Mortality rate has decreased in the last decade: 5% overall and 10–20% if severe
- Surgery if necrotic tissue present; hepatopancreato-biliary (HPB) surgeons to be involved early in cases of severe pancreatic necrosis
Pancreatitis: Later Complications

- 15–20% will develop serious complications
- May need consultation from ICU, nephrology, ID

1. **Acute fluid collections:**
   - Occur in early stages in 30–50%
   - Can progress to pseudocysts (no epithelial lining)

   **Treatment:**
   - Sterile acute fluid collections resolve spontaneously → therefore no treatment required
   - Infected collections → percutaneously drain + antibiotics

2. **Pancreatic and peripancreatic necrosis:**
   - Can be sterile or infected
   - Pasty or putty-like material – thick (i.e., will not come out with usual radiology drains)

   **Treatment:**
   - Sterile pancreatic necrosis → non-operative treatment with or without abdominal radiography
   - Surgery for persistent necrotizing pancreatitis should be as late as possible
     - Allows demarcation of necrotic tissue from viable parenchyma
     - Usually requires at least 4 weeks, but HPB surgeon must be involved EARLY
   - Infected necrosis → debridement + abdominal radiography with or without continuous lavage (i.e., via drains)
   - What surgeons need do:
     - Necrosectomy (cut out dead tissue and leave viable tissue)
     - Re-evaluation with regard to need for staged repeat laparotomies and repeat lavage
     - Closed continuous lavage of lesser sac and retroperitoneum
   - Often used and very helpful

3. **Pancreatic pseudocyst:**
   - Collections of pancreatic juice enclosed by nonepithelialized barrier
     - Composed of fibrous and granulation tissue
   - Can be located in intrapancreatic or extrapancreatic sites
   - Usually occur 4 to 6 weeks after pancreatitis (a defined wall needs to be created at this time)
   - Usually communicates with the ductal system
   - Large size can lead to mass effect or gastric outlet obstruction
   - Can erode into neighbouring vessel and cause pseudoaneurysm
     - Also referred to as “hemosuccus pancreaticus,” “upper GI bleed”

   **Treatment:**
   - Surgery currently the gold standard and is required for:
     - Cysts with complications (bleeds, pseudoaneurysms)
     - Cysts that persist for >6 weeks
     - Especially cysts >6 cm
   - Surgery involves:
     - Internal or external drainage
     - Distal pseudocystectomy with distal pancreatectomy
     - Cyst-gastrostomy (creating a stoma between cyst and stomach)
     - Or cyst-duodenostomy, or Roux-en-Y cyst-jejunostomy
   - Percutaneous drainage for only high-risk surgical patients
     - 60–90% success

4. **Pancreatic abscess:**
   - Collections of purulent fluid
   - Require drainage (as above)

5. **Pancreatic ascites and pancreatico-pleural fistulae:**
   - Following pancreatic duct damage or disruption, or from a leaking pseudocyst, where pancreatic juice flows freely into the peritoneal cavity and up around the lung

   **Treatment:**
   - Step 1: Non-operative treatment to decrease pancreatic secretions:
     - TPN, feeding tube, octreotide or somatostatin
   - Step 2: Identify the underlying pancreatic ductal disorder:
     - ERCP to determine approximate site of duct disruption
     - CT, MRCP to define anatomy more fully
   - Step 3: Repair the pancreatic ductal disruption:
     - ERCP/pancreatic sphincterotomy with or without placement of pancreatic duct stent (where possible and if safe)
     - Surgeon matches the procedure to the pathology
   - For example, distal pancreatectomy for distal ductal disruption
   - Pancreatico-cystenterostomy (to stomach or to roux-en-Y small bowel) for a ruptured pseudocyst

6. **Pancreatic aneurysms or rupture:**
   - 1–3% life-threatening hemorrhage
   - Erosion into the splenic artery

   **Treatment:**
   - Embolization or distal pancreatectomy

7. **Pancreatitis-induced splenic vein thrombosis:**
   - May result in gastroesophageal varices
**Treatment:**
- Splenectomy

**Indications for Surgical Intervention**
- Infected pancreatic necrosis
- Increasing toxicity
- Failure to improve despite continued support over a 3- to 4-week period
- Persistent peripancreatic mass on CT

- Acute abdominal catastrophe (e.g., bleeding with shock)

**Chronic Pancreatitis**
- Irreversible changes, including pancreatic fibrosis
- Loss of exocrine and/or endocrine pancreatic function
- 60–80% associated with alcohol abuse

**Clinical Presentation**
- Similar to acute pancreatitis

Figure 1. Classic Whipple procedure. **A**, Anatomy prior to Whipple procedure. The shaded area represents structures that are removed during surgery. The classic procedure removes 40% of the stomach, whereas the pylorus-preserving Whipple procedure preserves the pylorus (where the stomach empties into the duodenum). **B**, Organs removed during the Whipple procedure. **C**, Reconstruction of the pancreateo-duodenectomy with a Roux-En-Y (more common) or Billroth II configuration. Pancreateo-jejunostomy, choledocho-jejunostomy, and gastro-jejunostomy have been performed.
- Malabsorption (i.e., steatorrhea)
- Diabetes mellitus (insulin replacement required)
- Use of heating pads or hot water bottles leading to skin lesions
  - Erythema ab igne (also called “hot water bottle rash”; “toasted skin syndrome”)

Diagnosis
- CT □ pancreatic calcifications
- ERCP or MRCP □ irregularities in pancreatic ducts and areas of ductal dilation

Pancreatic Function Tests
- Serum amylase or lipase may or may not be elevated in chronic (compared with acute) condition
- Fecal tests
  - Fecal fat content to test for exocrine insufficiency (>7 grams [g] over 24 hours with 100 g fat diet)
  - Digestive enzymes (fecal elastase; serum trypsinogen)
- Tube tests (placement of collecting tube in duodenum)
  - Measuring pancreatic bicarbonate or enzyme output after meal or hormone stimulation of pancreas (either by secretin or cholecystokinin [CCK], and hence called “secretin-CCK test”)

Management
- Malabsorption
  - Cotazyme or pancrelipase (i.e., exogenous enzyme replacement) given with meals
- Pain
  - Medical management: abstinence from ethanol, pancreatic enzymes, somatostatin
  - ERCP: sphincterotomy and stenting
  - Radio-frequency ablation: percutaneous or endoscopic
  - Surgical options:
- Puestow procedure (as above)
- Distal pancreatectomy (as above)
- Whipple procedure (Pancreateico-duodenectomy) (Figure 1)
- Total pancreatectomy, islet auto-transplantation, and celiac plexus nerve block – one-stop definitive shop – very effective for pain control and can avoid long-term risks of diabetes (if not end stage)

Pancreatic Masses

Pancreatic Pseudocysts
- Discussed above (as a complication of pancreatitis)
- Is the most common type of pancreatic cyst (approximately 75%)
- Encapsulated collection of pancreatic secretions

Others Pancreatic Cysts to Consider
- Neoplastic cysts
- Intra-pancreatic mucinous neoplasms
  - IPMN is becoming increasingly recognized
  - Often found incidentally on cross-sectional CT or MRI
  - Can affect the main pancreatic duct or side-branches.
  - “Fish-mouth” ampulla leaking thick mucous fluid, seen on ERCP a classic finding
  - Major concern is of malignant transformation (to pancreatic carcinoma); can occur in up to 50% of cases
- An increasing indication for pre-emptive pancreatic resection
  - Serous cystadenomas (or microcystic adenomas) (SCA)
  - Intraductal papillary mucinous neoplasm

Malignant Pancreatic Masses
- 80–90% are ductal adenocarcinoma
- Far less commonly:
  - Mucinous noncystic carcinoma, signet ring cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, giant cell carcinoma; lymphoma
  - 3% of all GI malignancies, but >50 of periampullary tumours
  - High mortality due to lymphatic invasion in >50% at time of discovery
  - Only 20% of pancreatic carcinomas are candidates for surgical resection
  - The further the tumour is from the ampulla, the worse the prognosis
  - Patients usually present late
  - Turning yellow is NOT the first alarm symptom

Etiology
- Smoking
- Sporadic
- Chronic pancreatitis – 4% will progress to cancer within 20 years
- Dietary factors
  - Debatable but possibly associated with increased consumption of red meat or smoked meats; decreased intake of fruits and vegetables
- Diabetes –twofold increased risk
- Genetics
  - HNPCC gene (hereditary nonpolyposis colorectal cancer)
  - BRCA2 gene (breast cancer2, early onset)
  - Gardner syndrome (familial colorectal polyposis)

Clinical Presentation
- Three major symptoms: obstructive jaundice, duodenal
obstruction, and pain

- **Head**
  - Weight loss (92%)
  - Pain (72%)
  - Jaundice (82%), dark urine, light stools
  - Anorexia (64%)

- **Body or Tail**
  - Weight loss (100%)
  - Pain (87%)
  - Weakness (43%)
  - N/V, anorexia
  - Rarely, jaundice and obstructive symptoms

- **New-onset diabetes mellitus** (occasionally the presenting symptom)

- **Migratory thrombophlebitis** (Trousseau syndrome)
  - Tumour-induced hypercoagulable state

**On Examination**

- Signs of metastases
  - Courvoisier sign
    - Enlarged palpable non-tender gallbladder; unlikely due to stones
  - Malignant ascites
  - Peritoneal carcinomatosis

- Signs of lymph node spread
  - Sister Mary Joseph node (umbilicus)
  - Blumer shelf (on rectal examination)
  - Virchow/signal node (supraclavicular fossa; on left)

**Investigations**

- Elevated bilirubin, ALP

**Surgical Pearl: Contraindications to laparoscopic surgery**

Laparoscopic surgery is widely taught and widely applied and is increasingly used in emergency settings (including cholecystectomy and appendectomy). However, it is important to be aware of its relative contraindications:

- Circulatory shock or compromised cardiopulmonary status (peritoneal gas insufflation increases intra-abdominal pressure, which can cause hypotension)
- Markedly increased intracranial pressure (ICP) (it can cause it to worsen)
- Retinal detachment
- Ventriculo-peritoneal shunt
- Previous abdominal surgeries (may prevent safe entry into the abdomen due to adhesions)
- Pregnancy
- Inadequately equipped operating room

- Carcinoembryonic acid (CEA); CA 19-9
- CT; MRI
- Positron emission tomography (PET) (although not yet well established)
- ERCP (can identify periampullary or ampullary tumours, and expedite biopsy)

**Role of Biopsy**

- May be needed to guide palliative chemotherapy, but not if resection is planned

**CT Criteria for Resectability of Pancreatic Cancer**

1. Absence of extra-pancreatic disease
2. Absence of tumour involving or encasing the superior mesenteric, celiac, or hepatic arteries

**Preoperative Biliary Stenting**

- Indicated for highly symptomatic patients, especially if operation delayed
- Associated with a higher risk of postoperative infectious complications

**Palliative Surgery**

- Operative biliary bypass, gastric bypass, and splanchicectomy (gain access to splanchic nerves and inject 20 mL of 50% alcohol: each side of aorta; level of celiac axis)
- Biliary diversion can be performed via ERCP or percutaneously
- Gastric outlet obstruction
  - 10–15% pts and often pre-terminal event
  - Therefore, does not mandate correction if not proceeding to surgery
- Metastatic disease: survival 3–6 months survival
- Locally advanced: survival 6–12 months

**Treatment**

- Pancreatice-duodenectomy
  - More commonly known as “Whipple procedure” (see Figure 1)
  - Performed for head and uncinate tumours
  - Variations on Whipple procedure exist
  - Typical is en-bloc removal of the pancreatic head; the duodenum (which shares gastroduodenal artery supply with the pancreas head); a portion of CBD; the gallbladder, and the duodenum
  - Attempt by surgeon to preserve the pylorus
- To avoid “dumping syndrome” and improve functional outcomes
  - Anastomose remnants (i.e., three reconnections with the small bowel):
• Remnant pancreas and jejunum (pancreatico-jejunostomy)
• CBD and jejunum (choledocho-jejunostomy)
• Stomach (or pylorus-preserving) and jejunum (gastro-jejunostomy)
  - Major surgical risk pancreatic fistula
• May be controlled with drains, but occasionally repeat-operation required
• Adjuvant chemotherapy with or without radiation
  - 80% patients have recurrence with surgery alone
• No benefit from neoadjuvant therapy (i.e., chemotherapy to reduce tumour size prior to surgery)
• Locally advanced (arterial encasement or venous occlusion) chemotherapy with or without radiation
• Involvement of the portal vein or SMV; HPB surgeons will usually resect and reconstruct this vein; thus, tumour may be resectable
• If metastatic, chemotherapy

Complications
• Anastomotic leak (most likely from the pancreatico-jejunostomy due to pancreatic enzymes)
• Abscess
• Delayed gastric emptying (15–40%)
• Pancreatic fistula (15–20%)
• Diabetes mellitus

Carcinoma of the Ampulla
• Represents 1% of all GI malignancies
• Accounts for 15–25% of periampullary cancers
• Less than one-tenth as common as pancreatic cancer
• Adenoma (benign) carcinoma (malignant)
• May invade locally into the duodenum, pancreas, CBD
• Lymphatic spread is found in 30–50%

Signs and Symptoms
• Jaundice, weight loss, and epigastric pain
• Mechanical: gastric outlet obstruction
• 15% experience new onset diabetes mellitus in previous year
• Courvoisier sign (as above)
• Signs of lymph node spread (as above)
  - Sister Mary Joseph node (umbilicus)
  - Blumer shelf (on rectal exam)
  - Virchow/signal node (supraclavicular fossa)

Diagnosis
• CT
• MRI
• Upper GI endoscopy for duodenal carcinoma
• With or without ERCP, endoscopic US

Treatment Options
• Endoscopic snare excision of papilla
• Surgical transduodenal ampullectomy
• Whipple procedure or pancreatico-duodenectomy (see Figure 1)

References
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Annual Meeting 2015
October 14-17, 2015
Delta, PEI

Annual Meeting 2016
October 26-29, 2016
Westin, Montréal

Annual Meeting 2017
November 1-4, 2017
Hyatt Regency, Toronto

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Orthostatic Hypotension and Supine Hypertension in the Patient with Autonomic Failure

Maxime Lamarre-Cliche MD MSc

About the Author
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Summary
Orthostatic hypotension and supine hypertension are two cardiovascular symptoms of autonomic failure that can coexist in the same patient. Treatment of these conditions is difficult and needs to be tailored according to the objectives that should be set through a discussion with the patient.

Résumé
L’hypotension orthostatique et l’hypertension en position couchée sont des symptômes cardiovasculaires d’une défaillance du système nerveux autonome qui peuvent coexister chez le même patient. Leur traitement est complexe et doit être choisi en fonction d’objectifs établis en discussion avec ce dernier.

Upright posture forces about 500 mL of blood to be moved downward toward the lower limbs and abdominal capacitance vessels. Without regulatory mechanisms, the decrease in venous return results in a decrease in cardiac output and a symptomatic decrease in blood pressure (BP). The sympathetic system can be activated within seconds to counteract effects of gravity on cardiovascular homeostasis. In certain pathological states, the autonomic nervous system does not function appropriately and cannot adjust for exogenous influences on blood pressure. Accordingly upright posture will cause orthostatic hypotension (OH). Severe OH can cause many symptoms such as dizziness, fatigue, and syncope and it can be very debilitating. Because autonomic failure causes dysfunction of BP homeostasis, its impact on BP will not be limited to orthostatic hypotension. Supine hypertension is in fact present in most patients with autonomic failure and OH.1 OH is defined as a 20 mm Hg systolic or 10 mm Hg diastolic sustained decrease in BP when a patient goes from the supine to the upright posture. Supine hypertension is more difficult to define but relates to high BP in the supine position when BP is normal when seated or standing. There are no clear accepted definitions for supine hypertension but a 150 mm Hg systolic and 90 mm Hg diastolic BP thresholds when supine have been suggested.2

Autonomic failure with blood pressure disorders can be associated with many diseases but is mostly associated with primary neurodegenerative diseases namely Parkinson’s disease, multisystem atrophy and pure autonomic failure (Table 1). Whatever the cause, the impacts of autonomic failure on cardiovascular homeostasis are largely similar.

The prevalence of OH with or without supine hypertension due to autonomic failure is largely unknown. This prevalence can greatly vary with the definition of OH that may include or exclude patients that are non or slightly symptomatic. There are almost 100,000 patients with Parkinson’s disease in Canada3 and 30% of these patients have significant OH.4 Almost 30% of all elderly patients have OH5 but it is not clear how frequently this OH is clinically significant. One study suggests that more than half of patients with severe OH also present with supine hypertension.1
Table 1. Etiologies for Autonomic Failure

<table>
<thead>
<tr>
<th>Neurodegenerative diseases</th>
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<tbody>
<tr>
<td>Parkinson’s disease</td>
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<tr>
<td>Multiple system atrophy</td>
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<tr>
<td>Pure autonomic failure</td>
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<tr>
<td><strong>Metabolic, toxic</strong></td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>B₁₂ deficiency</td>
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<tr>
<td>Uremic neuropathy</td>
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<tr>
<td>Drug induced neuropathy</td>
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<tr>
<td>Alcohol induced neuropathy</td>
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<tr>
<td><strong>Auto immune</strong></td>
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<tr>
<td>Acute pandysautonomia</td>
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<tr>
<td>Lupus erythematosus</td>
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<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td><strong>Infectious causes</strong></td>
</tr>
<tr>
<td>Lyme disease</td>
</tr>
<tr>
<td>HIV infection</td>
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<tr>
<td>Neurosyphilis</td>
</tr>
<tr>
<td><strong>Inherited autonomic neuropathies</strong></td>
</tr>
<tr>
<td>Familial dysautonomia</td>
</tr>
<tr>
<td>Familial amyloid polyneuropathy</td>
</tr>
<tr>
<td>Hereditary sensitive autonomic neuropathy</td>
</tr>
<tr>
<td>Fabry disease</td>
</tr>
<tr>
<td>Acute intermittent porphyria variegated porphyria</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Spinal cord injuries</td>
</tr>
<tr>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Paraneoplastic autonomic neuropathy</td>
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<td>Holmes Adie syndrome</td>
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</table>

Clinical Importance of Orthostatic Hypotension and Supine Hypertension

OH has obvious consequences on functioning in the upright position. Patient complaints will range from slight dizziness when standing upright for long periods of time to syncopal with small orthostatic challenges. OH has also been identified as a marker of frailty and associated with an increase in mortality.²,³ There is lack of knowledge on the importance of supine hypertension in autonomic failure whether it is associated with OH or not. It has not been determined that supine hypertension in the patient with autonomic failure is associated with cardiovascular events or mortality but supine hypertension has been linked to left ventricular hypertrophy⁴ and loss of kidney function.⁵ There is no known threshold over which there is an impact on target organs. Because of this paucity of data, it appears appropriate to extrapolate from other populations such as essential hypertensive subjects. In these patients, the non-dipper phenotype defined as the absence of an appropriate decrease in BP at night has been associated with cardiovascular morbidity.⁶ It has been clearly shown that ambulatory BP monitoring is better than clinic BP measurements at identifying patients with high cardiovascular risk.⁷ Night time, day time and 24 hour blood pressure thresholds have been identified but it is not known if they can be applied to patients with autonomic failure. Ambulatory BP monitoring’s strength comes from averaging unbiased BP measurement over many hours. This as in essential hypertensives remains true in patients with supine hypertension due to autonomic failure.

Diagnostic Workup

The clinical evaluation of patients with OH should start with a thorough questionnaire oriented at the clinical manifestations of autonomic failure and OH and their impact on daily living. Cardiovascular symptoms should also be assessed. During the physical exam, BP and heart rate should be assessed supine and after standing 1, 2, and 3 minutes. The physical signs of hypertension target organ damage and of secondary hypertension should be looked for. Routine biochemistry, complete blood count, vitamin B₁₂, serum protein electrophoresis and an electrocardiogram should be obtained (Table 2). Rarely, urine or plasma metanephrines and catecholamines can be measured. They may help diagnose a pheochromocytoma that can induce high BP with OH or help identify neurodegenerative disorders with autonomic failure that are associated with very low catecholamine levels. Rarely, specific auto antibodies for autonomic failure (mainly ganglionic acetylcholine receptor auto antibodies) can be measured in patients with rapidly evolving unexplained autonomic failure. Ambulatory BP monitoring should be obtained in all autonomic failure patients with OH unless contra indicated. It offers unique insight on night-time BP and invaluable information on BP averages. The tilt table test is usually not necessary since OH can be easily demonstrated during the physical exam but it is useful when OH is suspected but cannot be demonstrated at the bedside and when it is necessary to safely measure orthostatic tolerance. This test aims to measure BP supine and during a 20 to 30 minutes stand using a dedicated table and BP and electrocardiographic monitors. Other tests can be used to measure the autonomic nervous system function. The deep breathing test and the Valsalva test measure the difference in heart rate with breathing or raised intrathoracic pressure. The cold pressor test measures the increase in BP with a painful stimulus. These tests are not done frequently because they add little to the management of blood pressure.
Treatment

Treatment of OH and supine hypertension begins with a clear definition of the therapeutic objectives. These objectives should be prioritized with the patient as it is not always possible to successfully reach every goal. OH objectives are symptom-based and have a strong quality of life component. Supine hypertension objectives are BP-based and rely heavily on ambulatory BP monitoring and self-measurements. The treatments for OH and supine hypertension will frequently evolve over time. Neurodegenerative diseases are frequently progressive, incidental co-morbidities or their treatment can have an impact on BP and OH symptoms, and exogenous factors such as outdoor temperature and diet changes can induce important changes in BP homeostasis. Chronopharmacology and pharmacodynamic properties of drugs will have a strong influence on the pharmacological solutions considered by the physician.

The level of evidence underlying the use of drugs for OH and supine hypertension is low and physician expertise is of importance in the treatment of these disorders.

OH and supine hypertension are two manifestations of the same disease and their treatments can interact but the differences in therapeutic objectives and in therapeutic modalities warrant separate discussions.

Treatment of Orthostatic Hypotension

Treatment of OH starts with non-pharmacological modalities (Table 3). Patients should abstain from activities during which orthostatic symptoms would put them at risk. They should also be careful with ambient heat, heavy meals and alcohol that can all have an exaggerated antihypertensive effect in autonomic failure patients. Patients should stay well hydrated and always keep a bottle of water at hand as 500 mL can increase BP within a few minutes. Salt intake should be encouraged unless supine hypertension is problematic. Caffeine can be used at meals to decrease the post prandial BP drop. Two cups of brewed coffee will contain a total of about 200 mg of caffeine and could increase systolic BP by more than 20 mm Hg. Compressive stockings that ideally go up to the waist can be of great help if they are tolerated. Head-of-bed elevation can theoretically increase morning blood volume and decrease orthostatic BP symptoms but a recent study has shown this treatment to be ineffective.

Pharmacological treatments for OH mainly rely on midodrine and fludrocortisone. Midodrine is a produg quickly metabolized into desglymidodrine by the liver. It is a peripheral alpha-1 receptor agonist that increases arterial resistance and venous return over a period of 3–4 hours. Randomized trials have demonstrated its hypertensive properties and clinical beneficial effects at dosages ranging from 2.5 mg to 10 mg given up to three times a day. Its adverse effects are mainly scalp pruritus, urinary retention, and supine hypertension. Midodrine’s short biological half-life helps in tailoring the pharmacological treatment to the patient’s needs. Fludrocortisone is a mineralocorticoid agonist with an 18 hour long biological half-life. It has been shown to increase BP by causing salt and water retention but there is no clinical trial that demonstrates its clinical benefits. It is nonetheless a well-known drug that it frequently used for treatment of OH at doses ranging from 0.1 to 0.4 mg daily. Adverse effects are oedema, decompensated heart failure, supine hypertension, and hypokalemia. About a third of elderly patients will not tolerate this drug.

The following treatments have been shown to have hypertensive properties but the evidence for their clinical benefits in OH is scant. Sodium tablets will increase water retention and BP but an increase in sodium intake can also be addressed through diet. Domperidone is a dopamine receptor antagonist that does not cross the blood-brain barrier. It has been shown to block to the hypertensive influences of levodopa in Parkinson’s patients. Recent warning about its

Table 2. Routine Tests for Orthostatic Hypotension and Supine Hypertension Due to Autonomic Failure

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
</tr>
<tr>
<td>Serum creatinine and electrolytes</td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
</tr>
<tr>
<td>Protein electrophoresis</td>
</tr>
<tr>
<td>Electrocardiogram</td>
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<tr>
<td>Ambulatory blood pressure monitoring</td>
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</table>

Table 3. Pharmacological Treatments for Orthostatic Hypotension

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Ranges and Usual Frequency</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midodrine</td>
<td>2.5 to 10 mg three times a day</td>
<td>++</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>0.05 to 0.4 mg daily</td>
<td>±</td>
</tr>
<tr>
<td>Domperidone</td>
<td>5 to 10 mg three times a day</td>
<td>±</td>
</tr>
<tr>
<td>Salt tablets</td>
<td>2 to 6 grams daily</td>
<td>0</td>
</tr>
<tr>
<td>Octreotide</td>
<td>25 to 100 µg sc before meals</td>
<td>±</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>50 U/Kg three times a week</td>
<td>±</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>30 to 60 mg twice a day</td>
<td>±</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>2.7 to 5.4 mg three times a day</td>
<td>±</td>
</tr>
<tr>
<td>Acarbose</td>
<td>25 to 100 mg three times a day</td>
<td>±</td>
</tr>
</tbody>
</table>

++: Moderate level of clinical evidence, ±: very low level of clinical evidence, 0: no formal clinical evidence
proarrhythmic influences limits its use though.\textsuperscript{25} Anti-inflammatory drugs can be used to increase BP by water and salt retention\textsuperscript{26} but have inherent adverse effects that can be troublesome. Erythropoietin has been shown to increase BP by increasing blood volume and can be used in patients with low hematocrits.\textsuperscript{27} Octreotide, a somatostatine analogue\textsuperscript{28–30} and acarbose, an alpha glucosidase inhibitor\textsuperscript{31} can reduce post prandial drop in BP by decreasing the release of digestive vasoactive peptides. Pyridostigmine\textsuperscript{32} and yohimbine\textsuperscript{26} can both increase sympathetic flow. Yohimbine may be more effective\textsuperscript{33} but the influence of both of the drugs on BP are still unclear.\textsuperscript{34} Ergotamine can increase BP\textsuperscript{35} but has potential ischemic adverse effects.

\textbf{Treatment of Supine Hypertension}

Nonpharmacologic treatment of supine hypertension is limited (Table 4). A reduced salt diet is theoretically pertinent but will be limited by its impact on OH. Head-of-bed elevation appears to be an elegant way of reducing supine BP but a recent study surprisingly did not confirm the antihypertensive properties of this treatment.\textsuperscript{17} Pharmacological treatments of supine hypertension need to be limited to the night-time period. Any antihypertensive treatment may increase OH and great care must be taken to decrease risks of falls. The first choice treatment is transdermal nitroglycerin. This drug has been shown to have strong antihypertensive properties in patients with autonomic failure. Small doses ranging from 0.025 to 0.2 mg/hr have been shown to have significant antihypertensive properties.\textsuperscript{1,2} It should be applied at bedtime and removed 1 to 2 hours before getting up in the morning. Calcium channel blockers have also been shown to be effective.\textsuperscript{2} Regular formulations should be selected to minimize residual morning influences. Diltiazem may be the most appropriate calcium channel blocker for this indication. Clonidine is another option that has been shown to decrease night-time BP in autonomic failure patients.\textsuperscript{36}

\textbf{Conclusion}

OH and supine hypertension are two cardiovascular symptoms of autonomic failure that can coexist in the same patient. Treatment of these conditions is difficult and needs to be tailored according to the objectives that should be set through a discussion with the patient. Non pharmacologic modalities and regular re-evaluation of all drugs with an impact on blood pressure should always precede introduction of BP modifying drugs. Pharmacologic treatment of OH and supine hypertension can coexist even if the objectives are different by nature. Regular re-evaluation of these treatments through time is essential to optimize patient benefits. Much clinical research is needed to better understand how available OH treatments improve quality of life and how supine hypertension treatments decrease target organ damage.

\textbf{Table 4. Pharmacological Treatments for Supine Hypertension}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose ranges and usual frequency</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal nitroglycerin</td>
<td>0.05 to 0.4 mg/hr night-time</td>
<td>+</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>30 to 120 mg at bedtime</td>
<td>+</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.1 mg at bedtime</td>
<td>+</td>
</tr>
</tbody>
</table>

+: Low level of clinical evidence

\textbf{References}

Adherence to Guidelines for Cardiac Catheterization Referrals and Secondary Prevention Strategies in Patients with Non-ST Segment Elevation Acute Coronary Syndromes

Michelle J. Haroun MD, Anjali Shroff MD, Joshua J. Manolakos MD, Madhu K. Natarajan MD MSc, John You MD MSc, Ameen Patel MD

Summary

Background: Previous studies have demonstrated higher referral rates for invasive procedures among patients admitted with acute coronary syndromes (ACS) to hospitals with catheterization facilities compared to those without. Studies have also reported underuse of evidence-based medical therapies and cardiac rehabilitation programs post myocardial infarction. We evaluated referral patterns for cardiac catheterization and use of secondary prevention strategies in current practice.

Methods: We conducted a retrospective study of 397 patients with non-ST segment elevation ACS, comparing angiography referrals at a hospital with on-site catheterization facilities (Site A, n = 194) versus a hospital without (Site B, n = 203). We also recorded the use of secondary prevention strategies including discharge medications, referrals to smoking cessation programs and cardiac rehabilitation.

Results: There was no significant effect of on-site angiography on the decision to manage patients invasively (adjusted OR for on-site angiography 1.49 95% CI 0.92-2.44, p = .11), or wait times for cardiac catheterization (Site A 1.9 days vs. Site B 2.2 days, difference −0.3 days, 95% CI −0.83 to 0.55, p = .70). However, at the time of hospital discharge, less than 70% of patients were prescribed dual antiplatelet therapy and only 13% of patients were referred for cardiac rehabilitation.

Conclusion: These observations suggest that in contemporary practice in a Southern Ontario community, the availability of on-site percutaneous coronary intervention does not influence referral rates or wait times for cardiac catheterization. However we did observe significant underuse of cardiac rehabilitation programs and certain medical therapies. This suggests that despite improvements in access to invasive procedures, there remain important gaps in secondary prevention of coronary artery disease, which represent opportunities to improve quality of care in these patients.
Patients with non-ST segment elevation acute coronary syndromes (ACS) represent a heterogeneous group with varying risk of death and ischemic complications. These patients should be risk stratified to determine the need for early revascularization versus a conservative approach with medical therapy alone.1 The Thrombolysis in Myocardial Infarction (TIMI) Risk score is a validated prognostication tool, which has shown to predict the risk of death and ischemic complications in patients with acute coronary syndrome.2 Despite the availability of risk stratification tools, there is wide variability in clinical practice regarding the decision to invasively manage patients with non-ST elevation ACS.3 Several studies have examined the impact of geographic location and availability of on-site angiography on referral patterns. These studies have consistently shown that patients admitted with ACS are more likely to undergo coronary angiography, and experience shorter wait times, if they are admitted to a hospital with on-site cardiac catheterization facilities.3–5 Studies have also shown that risk stratification tools are underutilized in the selection of an invasive versus conservative strategy.6

To our knowledge, there are no recent studies that have compared the referral patterns for cardiac catheterization at hospitals with and without catheterization facilities, according to initial risk assessment (e.g., Thrombolysis in Myocardial Infarction [TIMI] Risk score). The primary objective of this study was to examine the pattern of angiogram referrals in patients with non-ST elevation ACS based on the TIMI risk score at sites with and without catheterization facilities.

Despite recent advances in revascularization procedures, medical therapy remains as the cornerstone of treatment for coronary artery disease (CAD). Optimal use of medical therapy and risk factor modification strategies are still likely to be the most effective interventions with respect to mortality reduction in patients with CAD.6 A secondary objective of this study was
to investigate adherence to current guidelines for secondary prevention including use of evidence-based medical therapies, referrals to cardiac rehabilitation and smoking cessation programs.1

Methods

Study Setting

The study was conducted at two academic teaching hospitals in Hamilton, Ontario: Hamilton General Hospital (Site A) which has on-site catheterization facilities and St. Joseph’s Healthcare (Site B) which does not. This study was approved by the Hamilton Health Sciences and St. Joseph’s Healthcare Research Ethics Boards.

Patient Population

We performed a retrospective study of consecutive patients admitted to the two hospitals with a diagnosis of unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI) between January 2009 and October 2010. To investigate the impact of on-site cardiac catheterization availability on clinical decisions, patients were divided according to the presence (Site A) or absence (Site B) of such facilities at the admitting hospital. We included patients over the age of 18 years who had an emergency department (ED) diagnosis of ACS, NSTEMI, or UA. Exclusion criteria included: an ED diagnosis of ST elevation myocardial infarction (STEMI); ischemia refractory to nitroglycerin infusion; congestive heart failure (CHF) refractory to medical therapy; cardiogenic shock; patient refusal of cardiac catheterization; physician decision not to refer for cardiac catheterization based on patient comorbidities.

Table 1. Baseline characteristics of patients at Site A (on-site cardiac catheterization) and Site B (no on-site cardiac catheterization)

<table>
<thead>
<tr>
<th>Patient Demographics</th>
<th>Site A</th>
<th>Site B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>194</td>
<td>203</td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)*</td>
<td>66.1 (13.3)</td>
<td>68.4 (12.6)</td>
<td>.08</td>
</tr>
<tr>
<td>Median age</td>
<td>67</td>
<td>70</td>
<td>.09</td>
</tr>
<tr>
<td>Number of females</td>
<td>81 (41.8%)</td>
<td>101 (49.8%)</td>
<td>.13</td>
</tr>
<tr>
<td>Median TIMI score**</td>
<td>3</td>
<td>3</td>
<td>.19</td>
</tr>
<tr>
<td>Known coronary artery disease</td>
<td>123 (63.4%)</td>
<td>108 (53.2%)</td>
<td>.05</td>
</tr>
<tr>
<td>Previous cardiac catheterization</td>
<td>97 (50.0%)</td>
<td>68 (33.5%)</td>
<td>.003</td>
</tr>
<tr>
<td>Previous percutaneous coronary Intervention</td>
<td>56 (28.9%)</td>
<td>23 (11.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous coronary artery bypass graft</td>
<td>34 (17.5%)</td>
<td>23 (11.3%)</td>
<td>.12</td>
</tr>
<tr>
<td>Hypertension</td>
<td>142 (73.2%)</td>
<td>150 (73.9%)</td>
<td>.60</td>
</tr>
<tr>
<td>Diabetes</td>
<td>73 (37.6%)</td>
<td>69 (34.0%)</td>
<td>.70</td>
</tr>
<tr>
<td>Family history</td>
<td>51 (26.3%)</td>
<td>32 (15.8%)</td>
<td>.01</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>133 (68.6%)</td>
<td>122 (60.1%)</td>
<td>.10</td>
</tr>
<tr>
<td>Current smoker</td>
<td>47 (24.2%)</td>
<td>43 (21.2%)</td>
<td>.26</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>18 (9.3%)</td>
<td>30 (14.8%)</td>
<td>.12</td>
</tr>
<tr>
<td>ECG changes</td>
<td>26 (13.4%)</td>
<td>34 (16.7%)</td>
<td>.33</td>
</tr>
<tr>
<td>Troponin positive</td>
<td>38 (19.6%)</td>
<td>76 (37.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median creatinine</td>
<td>79.0</td>
<td>78.0</td>
<td>.55</td>
</tr>
</tbody>
</table>

SD = standard deviation; TIMI = thrombolysis in myocardial infarction.

Table 2. Predictors of referrals for cardiac catheterization

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
<th>*Adjusted Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG changes</td>
<td>6.87 (3.52 – 13.43)</td>
<td>&lt;.0001</td>
<td>5.44 (2.29-12.95)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Troponin +</td>
<td>3.90 (2.46 – 6.18)</td>
<td>&lt;.0001</td>
<td>3.91 (2.10-7.27)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cardiology consult or Cardiology MRP</td>
<td>3.78 (2.36 – 6.05)</td>
<td>&lt;.0001</td>
<td>2.85 (1.69-4.80)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TIMI risk</td>
<td>1.49 (1.27 – 1.74)</td>
<td>&lt;.0001</td>
<td>1.24 (1.02-1.52)</td>
<td>.03</td>
</tr>
<tr>
<td>Site (on-site PCI available)</td>
<td>1.32 (0.88 – 1.81)</td>
<td>.18</td>
<td>1.49 (0.92-2.44)</td>
<td>.11</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.98 – 1.01)</td>
<td>.35</td>
<td>1.00 (0.97-1.03)</td>
<td>.87</td>
</tr>
<tr>
<td>Gender (females)</td>
<td>0.51 (0.34 – 0.77)</td>
<td>.001</td>
<td>0.64 (0.40-1.02)</td>
<td>.06</td>
</tr>
<tr>
<td>Prior PCI or CABG</td>
<td>1.25 (0.82 – 1.91)</td>
<td>.298</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Known CAD</td>
<td>1.11 (0.74 – 1.66)</td>
<td>.62</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Prior cardiac catheterization</td>
<td>1.01 (0.67 – 1.51)</td>
<td>.975</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.99 (0.99 – 1.00)</td>
<td>.24</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, hospital site, TIMI risk, presence of ECG changes, troponin rise and involvement of Cardiologist (consult or most responsible physician)

CABG = coronary artery bypass graft; CAD = coronary artery disease; MRP = myeloid-related protein; PCI = percutaneous coronary intervention.
Data Collection
Data was abstracted from medical records by four trained investigators. Admission data included patient demographics, cardiac risk factors, the presence of ECG changes (≥0.5 mm ST segment deviation) and cardiac biomarkers (troponin T), serum creatinine, and admission medications. We used the chart-abstracted data to calculate the TIMI risk score for each patient.

We recorded referrals for non-invasive testing, cardiac catheterization and revascularization procedures. Wait times for cardiac catheterization and duration of hospital stay were recorded. The use of secondary prevention strategies was evaluated by recording discharge medications and referrals to cardiac rehabilitation as well as smoking cessation programs.

To ensure concordance between data extractors, all four investigators extracted data from a training set of 30 charts. Cohen’s kappa coefficient for the TIMI risk score was 0.77.

Statistical Analysis
We compared patient data at the two sites using the Student’s t test for continuous variables and the Fishers’ exact test for categorical variables. Referral rates for cardiac catheterization were compared across low (0–2), intermediate (3–4) and high (5–7) TIMI risk groups between the two sites using the Student’s t test.

We analyzed univariable associations of hospital site and cardiac catheterization referrals, TIMI risk score, serum creatinine, prior history of CAD, prior cardiac catheterization, and prior revascularization procedures. We used logistic regression to perform a multivariate analysis in order to evaluate the independent association between hospital site and angiogram referrals.

Results
Patient Population
A total of 397 patients were included in the study. Overall, patients at the two sites had a similar risk profile (median TIMI score of 3 at each site). The groups at each site were similar with respect to age, gender, and most risk factors for CAD (Table 1). However, patients admitted to Site A had higher rates of known CAD and prior revascularization procedures, while patients

Table 3: Rates of non-invasive testing, cardiac catheterization, and revascularization stratified by TIMI risk score

<table>
<thead>
<tr>
<th></th>
<th>Low Risk (0–2)</th>
<th></th>
<th>Intermediate Risk (3–4)</th>
<th></th>
<th>High Risk (5–6)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Site A</td>
<td>Site B</td>
<td>p</td>
<td>Site A</td>
<td>Site B</td>
<td>p</td>
</tr>
<tr>
<td>Number of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-invasive study</td>
<td>67</td>
<td>78</td>
<td></td>
<td>102</td>
<td>89</td>
<td>.37</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>27</td>
<td>20</td>
<td>.25</td>
<td>13</td>
<td>14</td>
<td>.64</td>
</tr>
<tr>
<td>*PCI</td>
<td>18</td>
<td>29</td>
<td>.02</td>
<td>55</td>
<td>29</td>
<td>.001</td>
</tr>
<tr>
<td>*CABG</td>
<td>1</td>
<td>2</td>
<td>.58</td>
<td>5</td>
<td>5</td>
<td>1.0</td>
</tr>
<tr>
<td>*Low risk coronary anatomy (normal or mild CAD)</td>
<td>9</td>
<td>10</td>
<td>.57</td>
<td>16</td>
<td>11</td>
<td>.40</td>
</tr>
</tbody>
</table>

*pPercentage of patients undergoing angiography
CABG = coronary artery bypass graft; CAD = coronary artery disease; PCI = percutaneous coronary intervention.

Table 4. Frequency of medication use at the time of discharge from each hospital site

<table>
<thead>
<tr>
<th>Medication</th>
<th>Site A (n = 81)</th>
<th>Site B (n = 115)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>68 (89.5%)</td>
<td>95 (91.3%)</td>
<td>.80</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>49 (64.5%)</td>
<td>69 (66.3%)</td>
<td>.87</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>62 (81.6%)</td>
<td>77 (74.0%)</td>
<td>.36</td>
</tr>
<tr>
<td>Statin</td>
<td>70 (92.1%)</td>
<td>91 (87.5%)</td>
<td>.46</td>
</tr>
<tr>
<td>Ace inhibitor</td>
<td>45 (59.0%)</td>
<td>66 (63.5%)</td>
<td>.54</td>
</tr>
<tr>
<td>Angiotensin Receptor blocker</td>
<td>9 (11.8%)</td>
<td>18 (15.7%)</td>
<td>.40</td>
</tr>
</tbody>
</table>

Figure 1. Wait times for angiography and total length of stay according to site.
admitted to site B had higher rates of positive cardiac biomarkers.

**Predictors of Cardiac Catheterization Referrals**

Overall, availability of on-site cardiac catheterization did not have a significant impact on catheterization referral rates (Table 2). The strongest predictors of cardiac catheterization referrals were the presence of ECG changes (adjusted OR 5.44, 95% CI 2.29–12.95, \( p < .0001 \)) and positive cardiac biomarkers (adjusted OR 3.91, 95% CI 2.10–7.27 \( p < .0001 \)).

**Cardiac Catheterization Referrals Stratified by TIMI Risk Score**

An invasive approach was selected in the majority of high-risk patients (TIMI>4), (Site A 72.0% vs. Site B 65.7%, \( p = .21 \)), with very few high-risk patients referred for noninvasive testing (Site A 8.0% vs. Site B 11.4%, \( p = .42 \)) (Table 3). Low risk patients (TIMI <3) were managed conservatively in most cases, but were more often referred for angiography at the site without PCI available (Site A 26.9% vs. Site B 37.2%, \( p = .03 \)). Intermediate risk patients (TIMI 3–4) were much more likely to be referred for angiography if admitted to the hospital with on-site catheterization facilities (Site A 53.9% vs. Site B 32.6%, \( p = .001 \)).

**Wait Times**

Among patients referred for cardiac catheterization, there was no difference in the time delay from referral date to the procedure date between the two sites (1.9 days at Site A vs. 2.2 days at Site B, \( p = .38 \)) (Figure 1). Overall, there was a trend towards a shorter length of stay for patients admitted to the hospital with on-site cardiac catheterization facilities, but this was not statistically significant (3.6 days at Site A vs. 4.2 days at Site B, \( p = .20 \)).

**Use of Secondary Prevention Strategies**

In our study, 89.5% and 91.3% of patients were discharged home on aspirin therapy from Site A and Site B, respectively. However, only 64.5% and 65.3% of patients were discharged on clopidogrel. The frequencies of medication use at the time of discharge are shown in Table 4.

Approximately 23% of included patients were identified as current smokers. However, only 12.8% (Site A) and 2.3% (Site B) of current smokers were referred to smoking cessation programs. Referral rates to cardiac rehabilitation programs were 11.5% and 14.5% at Site A and Site B respectively.

**Discussion**

In both the univariate analysis and adjusted analyses, we found no association between hospital site and the decision to refer patients for angiography. When stratified by TIMI risk group, most low risk patients were appropriately managed conservatively, while the majority of high-risk patients underwent angiography. Wait times for cardiac catheterization and total length of hospital stay did not differ significantly between sites. Our findings contrast with those of previous studies, which have identified hospital site as an important predictor of angiography referrals and total length of stay.\(^3\) This may reflect the impact of regional referral strategies and recent efforts to reduce wait times by the Cardiac Care Network (CCN) of Ontario. This working group was established in an effort to improve patient access to centralized cardiac care across the province in the last twenty years.

Overall, use of medical therapies was high in our study population. The use of aspirin, beta-blockers and ACE inhibitors or ARBs demonstrated an improvement in adherence to guidelines compared to previous studies which demonstrated aspirin use in less than 80% of patients, and the use of statins and ACE inhibitors in less than 50% of patients at hospital discharge.\(^7\)–\(^9\) Two-thirds of patients were prescribed dual antiplatelet therapy at the time of hospital discharge. Clopidogrel has been shown to reduce ischemic complications in patients with non-ST-segment elevation ACS who have dynamic ECG changes, positive cardiac biomarkers or who undergo revascularization.\(^10\) Less than 50% of patients in our study met these clinical criteria and therefore more selective use of clopidogrel was likely appropriate.

With regards to non-pharmacological, secondary prevention strategies, referral rates to cardiac rehabilitation and smoking cessation programs were extremely low at both hospitals. Cardiac rehabilitation in patients post myocardial infarction has been shown to reduce recurrent ischemic events and cardiovascular mortality.\(^11\),\(^12\) The low referral rates observed in our study suggest there is a need for education regarding the efficacy and availability of supervised exercise programs in patients with CAD. This might represent an opportunity to improve the quality of care in ACS patients.

**Limitations**

Our study has limitations as a result of its retrospective design and relatively small sample size. However, it is unlikely that a larger sample size would have significantly altered the main observations of this study. We observed a trend towards higher rates of angiogram referrals at the centre with on-site angiography, but this did not reach statistical significance. Perhaps a larger study would have demonstrated this difference to be significant, with more patients being referred at hospitals with on-site facilities. With this in mind, our study did demonstrate significant underuse of certain secondary
prevention strategies despite the limitations in sample size. Arguably, this message is of greater significance, as medical therapy is still the cornerstone of coronary artery disease management.

Conclusion

Our study showed that referrals for cardiac catheterization for patients with non-ST segment elevation ACS seem to be both timely and appropriate, regardless of availability of on-site cardiac catheterization. Use of evidence-based medical therapies in ACS has improved in comparison to previous reports. However, cardiac rehabilitation and smoking cessation programs were significantly underutilized. Although there have been significant improvements in access to invasive procedures, there remain important gaps in secondary prevention strategies which represent important opportunities to improve quality of care in these patients.

Funding

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References

Clinical Medicine: Advances in Implantable Cardiac Devices

Jorge Palazollo MD, Sheldon M. Singh MD

Introduction
The use of implantable cardiac devices has increased and will continue to increase as the population ages. For more than 50 years, patients with a slow pulse have enjoyed the benefits of cardiac pacing to alleviate symptoms and, in some cases, prolong life. Implantable cardiac devices have evolved; in addition to providing pacing support, some devices – namely, implantable cardioverter defibrillators (ICDs) – can also terminate malignant ventricular arrhythmias, facilitate the synchronization of ventricular function, monitor clinical variables, and store a wealth of information to assist clinical management. This review discusses currently available device diagnostics, highlights some advances in implantable cardiac device therapy, and provides a preview of future technologies that may improve the care of patients who have these devices.

Atrial Fibrillation
Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide. Patients with AF carry a threefold-to-fivefold increased risk of stroke. This risk is present even in patients with asymptomatic or subclinical AF.

Implantable cardiac devices, particularly those devices with a pacing lead within the atrium, can accurately detect atrial activity. Device diagnostics can allow one to make a precise diagnosis of AF, as well as quantify the duration of each episode and overall burden of the arrhythmia (Figure 1A). This information may provide guidance as to the need for oral anticoagulation, an important consideration given the economic impact of AF-related stroke. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT), which was reported in the New England Journal of Medicine, demonstrated that for patients with subclinical atrial arrhythmias lasting greater than 6 minutes, the odds of an ischemic stroke were 2.49.1

Figure 1. A, Atrial fibrillation burden, including the total time in atrial fibrillation and the number of episodes. B, Heart rate variability for a patient with congestive heart failure. AF = atrial fibrillation

About the Authors
When this article was written, Dr. Palazollo (far left) was a fellow in Cardiac electrophysiology and pacing at the Schulich Heart Program, Sunnybrook Health Sciences Center in, Toronto, Canada. Dr Palazollo completed his medical school, internal medicine and cardiology residency in Mendoza, Argentina. He subsequently completed basic cardiac electrophysiology Training at McMaster University, Hamilton, Ontario. Dr. Palazollo has a clinical interest in the care of patients with implantable cardiac devices. Dr. Sheldon Singh is a staff electrophysiologist and an assistant professor of Medicine in the Schulich Heart Program, Sunnybrook Health Sciences Centre, and is on the Faculty of Medicine at the University of Toronto. Correspondence may be directed to sheldon.singh@sunnybrook.ca.
Although further work is needed to determine whether oral anticoagulation may reduce this stroke risk, the provision of knowledge about the presence of subclinical atrial arrhythmias is an important feature of implantable cardiac devices. Clinicians should be aware of the value of this information, which can direct stroke reduction therapy. In addition to the ability to make decisions on the need for oral anticoagulation, the ability to accurately quantify the patient’s AF burden and average heart rate while in AF is also valuable to clinicians and ensures both adequate rate control and an appropriate response to anti-arrhythmic drugs.

**Congestive Heart Failure**

Despite advancements in medical therapy for congestive heart failure (CHF), the rates of CHF admissions have improved little in the past few decades. In the United States, half of all costs for CHF are related to in-hospital management. Additionally, readmission for CHF is not trivial; one-quarter of CHF patients require rehospitalization within 30 days of discharge. Implantable cardiac devices – specifically ICDs – obtain a vast wealth of clinical information that may be useful in the care of CHF patients and potentially reduce the need for hospitalization.

One approach to assessing the development of pulmonary congestion is to measure intrathoracic impedance. Simply stated, when an electrical current is passed across the lung (by pulsing energy from the lead placed in the heart to the pulse generator located in the chest wall), the impedance to this flow of current can be determined. With the development of pulmonary congestion, this impedance will drop, as fluid has better conductance than air. Monitoring day-to-day changes in impedance may allow one to identify the early onset of pulmonary congestion and may – through prompt treatment – avert a hospital admission.

The measurement of heart rate variability is yet another way to assess the severity of CHF and changes in the status of patients with CHF (Figure 1B). Simply stated, heart rate variability is the beat-to-beat variability in consecutive QRS intervals. Worsening heart failure is associated with increased sympathetic activation, higher levels of circulating catecholamines, and a reduction in the normal heart rate variability; these have been correlated with reduced survival. Reduced HR variability is an important indicator for intensification of care in this patient population.

Other physiologic information about progressive CHF is captured by implantable cardiac devices; this includes information on the burden of arrhythmias (both atrial and ventricular) and on elevated nocturnal heart rates. Having this information may allow clinicians to identify patients at higher risk, who might benefit from treatments that will keep them well and out of hospital.²

New, more precise hemodynamic assessments with pressure sensors directly monitoring the left atrial and the pulmonary arterial pressure will be available. The CHAMPION study assessed the role of clinician-guided management of CHF patients by direct pulmonary arterial pressure monitoring with the CardioMEMS pulmonary artery pressure monitor.³ Results showed a large reduction (HR = 0.72) in hospitalizations of patients with CHF managed with this device. The use of novel and existing tools may have a significant role in improving the care of patients with CHF.

**Remote Monitoring**

Accessing the wealth of information available from cardiac devices, particularly for day-to-day monitoring, would be cumbersome if the data could be accessed only as it has been traditionally – that is, with patients visiting their local device clinic. The time and cost associated with this would likely be a deterrent to accessing and utilizing this information for routine clinical use. Device-based algorithms are used in an attempt to overcome this barrier; programmable algorithms are available in implantable devices that inform patients of adverse events by audible alerts or alarms, prompting the patients to seek medical care.

Recently, remote monitoring has become available, bringing patients and caregivers closer (Figure 2). Home bedside transmitters can communicate wirelessly with a patient’s implantable device, download information, and transmit that information to a central secure website accessible to caregivers. This approach not only provides some safety regarding device malfunction but can also provide caregivers access to the clinical diagnostics described above, thereby allowing more-
Tailored patient care. Evidence indicates that this approach does accelerate the identification of new clinical events. Data collection and storage, patient confidentiality, and caregiver responsibilities for acting on the data are currently being addressed at centres that employ this technology.4

New Devices

**Magnetic Resonance Imaging Conditional Devices**

Currently, the presence of implantable cardiac devices is considered to be a relative contraindication to magnetic resonance imaging (MRI). This may be problematic, as a large proportion of patients with an implantable device may require MRI during their lifetime. Several concerns arise with MRI of patients with implantable cardiac devices. These include the torque placed on the lead in the magnetic field, which may result in lead dislodgement; pacing behaviours that may change when exposed to a strong magnet; and lead heating, which may injure the adjacent cardiac tissue or actually stimulate the heart. Magnetic resonance imaging–conditional cardiac devices (both pacemakers and defibrillators) are now available. Currently, Health Canada approves MRI-compatible pacemakers for routine use, whereas MRI-compatible ICDs are available under the Special Access Program. These newer devices have less ferromagnetic components which make movement within the MRI field less likely, and have been shown to cause no increased risk in patients undergoing scanning with a 1.5 tesla scanner. Additional data on the safety of scanning with higher-power magnets is necessary, but the general notion is that these devices are likely safe.5

**Leadless Pacemakers**

Leads are an important – if not the most important – component of pacing systems, because this portion of the device facilitates cardiac pacing and is used to derive information on clinical events. Unfortunately, leads are considered the weakest link of an implantable cardiac device system, as they are exposed to mechanical stress with cardiac and thoracic wall motion. This can result in lead fracture or a breach of insulation. In addition, the risks associated with acute lead implantation, including the risk of pneumothorax or cardiac perforation, are not trivial. Chronic issues that are associated with lead placement within the vascular system include venous occlusion, thrombus formation, and bacterial seeding (of which the resulting device infection can be catastrophic). Such issues are particularly important for young patients who are receiving implantable devices, which expose these patients to a long-term risk of lead complications and the associated morbidity.

Leadless pacemakers have recently been developed and are currently being evaluated in the clinical arena (Figure 3A).6 Unlike a pulse generator implanted in the chest wall (with accompanying leads placed within the heart), a leadless pacemaker is a self-contained device with battery, diagnostic, and pacing functions. The device is delivered through a large delivery sheath from the femoral vein and screwed into the heart; once positioned, the device remains tethered to the heart. These devices, which are less than 10% the size of traditional pacemakers, can perform the same functions that are performed by pacemakers and can avoid the need for leads.
Subcutaneous Defibrillators

The desire to minimize implantable hardware has also resulted in the development of a defibrillator that does not need transvenous leads. The totally subcutaneous implantable defibrillator is approved by the US Food and Drug Administration and is available through the Health Canada Special Access Programme (Figure 3B). Preliminary studies have shown that this device may sense malignant ventricular arrhythmias in a manner similar to that of a traditional defibrillator and may provide life-saving therapies; however, there are some lingering concerns. Additionally, the absence of any intravascular component has resulted in an inability to provide pacing for those patients who may require pacing capacity in addition to the capability to terminate malignant ventricular arrhythmias.

Conclusion

Implantable cardiac devices can improve the patient’s symptoms and the quality and length of his or her life. Work aiming to improve on device designs that reduce device-related complications is ongoing. Furthermore, advances in software and device algorithms to detect subclinical arrhythmia and the monitoring of other related conditions will provide even better clinical outcomes for patients with implanted cardiac devices.

References

Expert Consensus on a Canadian Internal Medicine Ultrasound Curriculum

By The Western Canadian Internal Medicine Ultrasound Curriculum Committee
(Shane Arishenkoff MD, Marcus Blouw MD, Sharon Card MD, John Conly MD, Colin Gebhardt MD, Neil Gibson MD, Ryan Lenz MD, Irene W. Y. Ma MD, Graydon S. Meneilly MD, Leanne Reimche MD, Jeffrey Schaefer MD, Michael Sochocki MD, and Kelly Zarnke MD)

Summary
Ultrasonography is increasingly used at the bedside. In the absence of an already developed curriculum appropriate for Canadian internal medicine training programs, 13 representatives from internal medicine programs in five Western Canadian provinces met for 2 days to develop and propose a consensus-based internal medicine curriculum for training in the bedside use of ultrasonography in a Canadian health care context. All 13 had had interest or leadership role in those programs. The curriculum’s content was based on three overarching principles agreed upon by the group: (1) content should be selected on the basis of clinical or educational need; (2) content should be feasible (i.e., both cognitive and technical components of the curriculum could be reasonably taught and learned in a competency-based manner while minimizing potential risks to patients); and (3) content should be evidence based. A consensus-based curriculum of 16 proposed topics is to be considered for the core internal medicine residency training program (postgraduate year [PGY] 1 to PGY 3), and 22 topics are to be considered for general internal medicine subspecialty training programs (PGY 4 to PGY 5).

About the Authors
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Résumé
L’échographie est de plus en plus utilisée dans les soins aux patients. En l’absence d’un cursus adéquat en échographie dans les programmes canadiens de formation à la médecine interne, treize représentants ayant un intérêt ou jouant un rôle de leadership dans ces programmes dans chacune des cinq provinces de l’Ouest se sont rencontrés pendant deux jours afin d’élaborer et de proposer un cursus consensus en échographie pour la formation des internistes dans le contexte des soins de santé au Canada. Le groupe de travail s’est donné trois grands principes pour établir le contenu du programme : 1) il doit répondre à des besoins cliniques ou pédagogiques; 2) il doit être possible de le transmettre (ses éléments cognitifs et techniques peuvent raisonnablement être enseignés et appris dans le cadre d’un enseignement axé sur les compétences, avec un risque potentiel minime pour les patients); 3) il doit être basé sur des données probantes. Nous présentons ici un cursus consensus comptant 16 propositions à intégrer dans le tronc commun du programme de formation des résidents en médecine interne (R1 à R3) et 22 propositions pour les programmes de formation en sous-spécialité de médecine interne générale (R4 et R5).
Keywords
bedside ultrasound; consensus, curriculum content; evidence-based; internal medicine program

Over the past decade, bedside ultrasound has been increasingly used by nonimaging specialists, including emergency physicians, obstetricians, and critical care specialists. Ultrasoundography can be used as a preclinical tool to improve the understanding of anatomy, physiology, and pathology. Alternatively, it can be used as a clinical tool in making diagnoses at the bedside. For example, as a preclinical or educational tool, ultrasoundography may help learners improve their physical examination techniques (such as those for examining the liver), and it may be used clinically as a diagnostic tool (e.g., for ruling out pneumothoraces). This increasing recognition of the role of point-of-care ultrasound at the bedside, as well as its role as a standard of care in assisting procedural skills such as central venous catheterization, highlights the relevance of clinical ultrasonography to internal medicine training and practice. However, proper training in its use is necessary. It is increasingly difficult to ignore the need for a defined internal medicine curriculum in regard to what ultrasonographic skills are important for delivering effective care to our patients. At a minimum, postgraduate training programs need to meet the objectives of training put forth by their accrediting bodies (e.g., the Royal College of Physicians and Surgeons of Canada). These typically include competency in placing central venous catheters and in performing a variety of diagnostic and therapeutic bedside procedures. For a number of these procedures, there is accumulating evidence that supports the use of ultrasound guidance for improving procedural safety. Programs that teach these procedures should implement appropriate training in, and assessment of, the use of ultrasound guidance. Further applications of ultrasound may include its use in diagnostic assessments and as an educational tool (e.g., the use of ultrasound to provide visual feedback to enhance physical examination skills or to increase the understanding and knowledge of physiology and anatomy).

What to include in an ultrasonography curriculum appropriate for training in internal medicine has not yet been defined. There are a number of competing interests and demands, including the improvement of patient safety and the need to prepare residents for continuing training in subspecialties that require bedside ultrasound and an understanding of its uses and limitations. Practical considerations include the ability of existing practicing and teaching faculty to acquire, deploy, and teach bedside ultrasound skills; budgetary concerns; patient privacy issues regarding the storage of images; and availability of time to learn ultrasonographic skills within an already full internal medicine educational curriculum. A frequent and important concern among educators is the potential for eager but naive adopters of the technology to use novice skills beyond the intended scope of such skills, resulting in harm to patients. Therefore, educators designing a curriculum must be mindful of potential risks and benefits, educational values, and unintended consequences.

In the absence of any already developed curriculum appropriate for Canadian internal medicine training programs, we sought to develop and propose a consensus-based internal medicine curriculum for bedside ultrasound use in the Canadian health care context.

Methods
Internal medicine program representatives with an interest or leadership role in each of the four Western Canadian provinces (British Columbia, Alberta, Saskatchewan, and Manitoba) were identified by their respective programs and invited to partake in a 2-day meeting held at the University of Calgary on June 10–11, 2013. Each invited member had previous training or experiential knowledge regarding the use of ultrasound in internal medicine. Although individual members of the working group have leadership roles locally, nationally, and internationally, this document reflects a consensus of individual opinions and is not intended to reflect the leadership groups to which the individuals belong.

Prior to the meeting, existing guidelines for ultrasonography practice and a training curriculum in emergency and critical care medicine were circulated among the participants. These guidelines covered a variety of topics, such as standards for ultrasound equipment, examination-specific guidelines, the safe use of ultrasound, the use of ultrasound in procedures, and training and practice standards.

On the first day of the meeting, participants discussed and agreed upon the overarching principles by which curriculum content would be selected. In the first round of discussion, a comprehensive list of candidate topics was created on the basis of the experience, knowledge, and interests of the attendees. The entire group was then divided at random into three working groups; each working group discussed and evaluated the proposed candidate topics. A preliminary discussion was held on whether a topic needed to be, should be, or could be included in the internal medicine curriculum, or whether it should not or could not be included in the curriculum. On the basis of the group response to candidate topics, each topic was searched on
MEDLINE with the search terms “ultrasound,” “ultrason$$,” and “point of care,” as well as with terms related to the topic. Evidence on each candidate topic was then presented again to all participants.

On the second day, a modified Delphi technique was used to obtain a consensus on the content of a curriculum for internal medicine residency training programs. In a blinded fashion, participants voted for inclusion versus exclusion of content in the curriculum. Participants were also asked to indicate if the specific topic should be used for teaching physical examination, making a clinical diagnosis, or guiding procedures. Additional rounds of votes and discussion were repeated in an unblinded fashion until participants reached a consensus (≥80% agreement) on the topics chosen for inclusion. The entire group then voted on these topics in an unblinded fashion on their appropriateness for inclusion in the core internal medicine program (by the end

<table>
<thead>
<tr>
<th>Topic No.</th>
<th>Category</th>
<th>Potential Topic</th>
<th>Votes for Inclusion (%)</th>
<th>Consensus* for Further Consideration</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>Volume status</td>
<td>Internal jugular vein height</td>
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<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Volume status</td>
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</tr>
<tr>
<td>3</td>
<td>Fluid collections</td>
<td>Pleural</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Fluid collections</td>
<td>Ascites</td>
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<td>Yes</td>
</tr>
<tr>
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<td>Fluid collections</td>
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<td>Renal</td>
<td>Hydrenephrosis</td>
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</tr>
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<td>7</td>
<td>Cardiac</td>
<td>Left ventricular function (gross)</td>
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</tr>
<tr>
<td>8</td>
<td>Cardiac</td>
<td>Right ventricular function (gross)</td>
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</tr>
<tr>
<td>9</td>
<td>Liver/spleen</td>
<td>Span</td>
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</tr>
<tr>
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<td>Head and neck</td>
<td>Thyroid</td>
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<td>Consolidation</td>
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<td>No</td>
</tr>
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<td>Pneumothorax</td>
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<td>14</td>
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<td>Abscess/cellulitis</td>
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</tr>
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<td>15</td>
<td>Soft tissue</td>
<td>Joint effusion</td>
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<tr>
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<td>Intracranial pressure</td>
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<td>18</td>
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<td>Aortic dissection</td>
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<tr>
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<td>Lymphadenopathy</td>
<td>3 (23)</td>
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<tr>
<td>22</td>
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<td>Bladder</td>
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</tr>
<tr>
<td>23</td>
<td>Biliary tree</td>
<td>Cholelithiasis</td>
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</tr>
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<td>24</td>
<td>Biliary tree</td>
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<td>25</td>
<td>Minors</td>
<td>Fetal</td>
<td>0 (0)</td>
<td>No</td>
</tr>
<tr>
<td>26</td>
<td>Minors</td>
<td>Children aged &lt; 16 yr</td>
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<tr>
<td>27</td>
<td>Procedures</td>
<td>Central venous catheterization – internal jugular vein</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>28</td>
<td>Procedures</td>
<td>Central venous catheterization – subclavian vein</td>
<td>10 (77)</td>
<td>No</td>
</tr>
<tr>
<td>29</td>
<td>Procedures</td>
<td>Central venous catheterization – femoral vein</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>30</td>
<td>Procedures</td>
<td>PICC</td>
<td>12 (92)</td>
<td>Yes</td>
</tr>
<tr>
<td>31</td>
<td>Procedures</td>
<td>Arterial line insertion</td>
<td>12 (92)</td>
<td>Yes</td>
</tr>
<tr>
<td>32</td>
<td>Procedures</td>
<td>Peripheral intravenous access</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>33</td>
<td>Procedures</td>
<td>Thoracentesis</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>34</td>
<td>Procedures</td>
<td>Paracentesis</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>35</td>
<td>Procedures</td>
<td>Lumbar puncture</td>
<td>10 (77)</td>
<td>No</td>
</tr>
<tr>
<td>36</td>
<td>Procedures</td>
<td>Joint aspiration</td>
<td>12 (92)</td>
<td>Yes</td>
</tr>
<tr>
<td>37</td>
<td>Procedures</td>
<td>Abscess aspirate sampling</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>38</td>
<td>Procedures</td>
<td>Abscess incision and drainage</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

PICC = peripherally inserted central catheter.

* > 80% agreement.
of postgraduate year 3 (PGY 3]) and for internal medicine or general internal medicine subspecialty training (at the end of PGY 4 or PGY 5).

### Results
Thirteen individuals participated in the process: two from the University of British Columbia, one from the University of Alberta, six from the University of Calgary, two from the University of Saskatchewan, and two from the University of Manitoba. The internal medicine specialties that were represented included general internal medicine, critical care medicine, infectious disease, nephrology, respirology, and geriatrics. Participants included one current and one former chair of an internal medicine department, one core residency program director, one former program director for PGY 4 and PGY 5 trainees going into general internal medicine (GIM) practice, one GIM division head, five faculty/departmental leaders in ultrasonography training, and two postgraduate trainees in their final 2 years of subspecialty training.

Three principles of curriculum content were agreed upon by the group: (1) content should be selected on the basis of clinical or educational need; (2) content should be feasible (i.e., both cognitive and technical components of the curriculum content can be reasonably taught and learned in a competency-based manner while minimizing potential risks to patients); and (3) content should be evidence based (showing evidence of educational utility and/or improved outcomes).

The group considered 38 topics (Table 1) and selected 22 for further consideration. The group’s members unanimously felt that fetal scans on pregnant patients and non-medically indicated scans on children (such as those done simply for training purposes) should not be performed by trainees. Although ultrasound is generally considered to be safe, sound waves do pose concerns about thermal and nonthermal safety.25,26 As such, all users are required to adhere to the “as low as reasonably achievable” (ALARA) principle.25 The potential bioeffects are of

### Table 2. Final Consensus of 13 Participants on 22 Topics Proposed for Inclusion in Provisional Internal Medicine Curriculum

<table>
<thead>
<tr>
<th>Topic</th>
<th>Votes for Inclusion in Core IM Curriculum (%)</th>
<th>Consensus+ to Include in Core IM Curriculum</th>
<th>Votes for Inclusion in GIM Subspecialty Curriculum (%)</th>
<th>Consensus+ to Include in GIM Subspecialty Curriculum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal jugular vein height</td>
<td>13 (100)</td>
<td>Yes</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>Inferior vena cava measurement</td>
<td>12 (92)</td>
<td>Yes</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>13 (100)</td>
<td>Yes</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>13 (100)</td>
<td>Yes</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>Liver and spleen span</td>
<td>13 (100)</td>
<td>Yes</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>Ascites</td>
<td>13 (100)</td>
<td>Yes</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>Bladder</td>
<td>12 (92)</td>
<td>Yes</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>Abscess/cellulitis</td>
<td>12 (92)</td>
<td>Yes</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>Central venous catheterization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– internal jugular vein</td>
<td>13 (100)</td>
<td>Yes</td>
<td>13 (100)</td>
<td>Yes</td>
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<tr>
<td>Central venous catheterization</td>
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<td></td>
</tr>
<tr>
<td>– femoral vein</td>
<td>13 (100)</td>
<td>Yes</td>
<td>13 (100)</td>
<td>Yes</td>
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<td>Arterial line insertion</td>
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<td>Peripheral intravenous access</td>
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<td>13 (100)</td>
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<tr>
<td>Thoracentesis</td>
<td>13 (100)</td>
<td>Yes</td>
<td>13 (100)</td>
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<td>Paracentesis</td>
<td>13 (100)</td>
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<td>13 (100)</td>
<td>Yes</td>
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<tr>
<td>Joint aspiration</td>
<td>11 (85)</td>
<td>Yes</td>
<td>13 (100)</td>
<td>Yes</td>
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<td>Abscess aspirate sampling</td>
<td>13 (100)</td>
<td>Yes</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>Abscess incision and drainage</td>
<td>9 (69)</td>
<td>No</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>PICC</td>
<td>5 (38)</td>
<td>No</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>Pulmonary edema</td>
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<td>No</td>
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<td>Yes</td>
</tr>
<tr>
<td>Left ventricular function (gross)</td>
<td>6 (46)</td>
<td>No</td>
<td>13 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>Right ventricular function (gross)</td>
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<td>No</td>
<td>13 (100)</td>
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<tr>
<td>Pericardial effusion</td>
<td>7 (54)</td>
<td>No</td>
<td>13 (100)</td>
<td>Yes</td>
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</tbody>
</table>

IM = internal medicine; GIM = general internal medicine; PICC = peripherally inserted central catheter.

*Core internal medicine (PGY 1 to PGY 3) or internal medicine/general internal medicine subspecialty (PGY 4 to PGY 5).
Consensus on a Canadian Internal Medicine Ultrasound Curriculum

particular concern in high-attenuation tissues such as fetal and growing bones.\textsuperscript{27,28} As a result, Health Canada, for non-medical reasons, does not recommend ultrasound for obstetrical use.\textsuperscript{26} Other topics were rejected because of the potential difficulty in teaching and learning them, the potential medico-legal risk, the low likelihood that an acquired skill would lead to changes in management, and the possibility of their being beyond an internist's scope of practice.

Of the 22 included topics, 16 were felt to be potentially suitable for inclusion into a core internal medicine training program (Table 2). Three Delphi rounds were conducted to reach a consensus. These 16 topics included measurement of the height of the internal jugular vein,\textsuperscript{29,30} inferior vena cava measurement,\textsuperscript{31,32} pleural effusion and thoracentesis,\textsuperscript{8,33,34} central line insertion and pneumothorax,\textsuperscript{3,6,7,35,36} liver and spleen examination,\textsuperscript{2,3,7} ascites and paracentesis,\textsuperscript{9,38} the bladder,\textsuperscript{14,39,40} cellulitis/abscess/aspirates,\textsuperscript{41,42} arterial line insertion,\textsuperscript{43} peripheral intravenous access,\textsuperscript{44,45} and joint aspiration.\textsuperscript{10} Although the evidence for the role of ultrasound in establishing peripheral intravenous access in adults is not as consistent as that in pediatric patients,\textsuperscript{46} the group felt that learning this skill is unlikely to be harmful and may improve the care of patients.

All 22 topics were deemed potentially suitable for a GIM subspecialty curriculum. The additional topics included abscess incision and drainage,\textsuperscript{41,42} peripherally inserted central catheters,\textsuperscript{16} pulmonary edema,\textsuperscript{47} and focused and limited cardiac examination.\textsuperscript{48–50}

Discussion

This is the first consensus-based report on potentially appropriate curriculum content for inclusion into Canadian internal medicine training programs that is mindful of educational, patient safety, and evidence-based principles. Our committee recommends that the 16 proposed topics should be considered for the core internal medicine residency training program (PGY-1 to PGY-3) and that 22 topics be considered for training programs in the general internal medicine subspecialty. Fetal scans on pregnant women and scans on children should not be performed by trainees.

Our report has a number of limitations. First, it is based on expert opinion-based consensus and preliminary evidence only; we did not conduct a comprehensive systematic review using multiple databases on each of the candidate topics. Second, our first meeting was limited in scope, in that our group’s members represented only the Western provinces; we did not intend to be exclusive, but owing to practical and feasibility issues, we began with a smaller regional group of centres. Third, although we aimed to adhere to educational, patient safety, and evidence-based principles, the contribution of any curriculum to overall patient safety must ultimately be mindful of content, modes of curriculum delivery, assessment, and program evaluation. Our report does not specify the approach to the curriculum’s delivery and implementation (e.g., who teaches, how teaching is done, and the exact content of the curriculum within a topic); consequently, each centre’s experience will vary. Fourth, the proposed topics are intended only to be a starting point for curriculum design and should not be followed in a prescriptive manner. Last, we did not address device technology and its affordability or availability. Individual members of the working group have varied experiences with different types of ultrasound devices, but addressing which specific device functionalities training programs should provide is currently beyond the scope of the working group.

Future Directions

At its next meeting, the group intends to share further institutional experiences, discuss teaching resources and continuing professional development workshops for faculties, and set definitions of minimal competence for select skills. Further, the group plans to discuss potential research ideas that will assist the delivery of further evidence-based medical education in the use of ultrasonography in internal medicine.

Acknowledgements

We wish to thank Maureen Sorensen, Lori Miller, and Deb Hewko for their assistance with our first meeting. The participants also wish to thank the W21C (Ward of the 21st Century), the University of Calgary, and the University of Calgary’s Division of General Internal Medicine for hosting the meeting.

References

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Löfgren Syndrome Developing during Infliximab Therapy for Crohn's Disease: A Case Report

Isabel Coman MD, J. Manuel Dominguez MD, Annie Belisle MD

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Summary
Tumour necrosis factor alpha (TNFα) antagonists are biological response modifiers increasingly used to effectively treat a wide array of inflammatory diseases such as Crohn's disease and rheumatoid arthritis. Anti-TNFα agents are also used in the treatment of steroid-refractory granulomatous diseases, with reported success. Paradoxically, an increasing number of cases of anti-TNF-induced sarcoidosis are being reported. The acute form of sarcoidosis, Löfgren syndrome, is characterized by mediastinal adenopathy, erythema nodosum, arthralgia, and fever. This article describes the case of a patient with Crohn's disease who developed Löfgren syndrome during treatment with infliximab. To our knowledge, this is the first case of Löfgren syndrome developing during treatment with a TNFα antagonist.

Résumé
Les antagonistes du facteur de nécrose tumorale alpha (TNFα) sont des modificateurs de la réponse biologique de plus en plus employés pour traiter efficacement toute une gamme de maladies inflammatoires, dont la maladie de Crohn et la polyarthrite rhumatoïde. Les anti-TNFα sont aussi utilisés avec succès dans le traitement des maladies granulomateuses réfractaires aux stéroïdes. Paradoxalement, on signale un nombre croissant de cas de sarcoïdose induite par les anti-TNF. La forme aiguë de la sarcoïdose, le syndrome de Löfgren, se caractérise par une adénopathie médiastinale, des érythèmes noueux, de l’arthralgie et de la fièvre. Nous décrivons ici le cas d’une patiente atteinte de la maladie de Crohn qui a développé le syndrome de Löfgren pendant un traitement à l’infliximab. À notre connaissance, il s’agit du premier cas de syndrome de Löfgren à survenir pendant l’administration d’un antagoniste du TNFα.

Clinical Notes
A 56-year-old woman presented to the emergency room after two weeks of experiencing progressive dyspnea and a dry cough. She had a 35-year history of Crohn's disease and had had a colectomy at 28 years of age. She had suffered recurrent episodes of pouchitis, which, due to infliximab, was in clinical remission. Two months after starting treatment, she developed painful subcutaneous nodules on the lower limbs and around the elbows, arthralgia in the knees, increasing fatigue, and occasional fever. Her gastroenterologist discontinued anti-TNF treatment and referred her for a skin biopsy; this showed granulomatous inflammatory infiltrates in the deep subcutaneous fat, with giant cells, histiocytes, and few lymphocytes (Figure 1). Necrosis was not present. The differential diagnosis included atypical erythema nodosum, atypical sarcoidosis, and cutaneous Crohn's disease.

Blood tests revealed a sedimentation rate of 30 mm/h, a C-reactive protein level of 20 mg/L, an elevated angiotensin-converting enzyme (ACE) level of 134 U/L (N < 8–52), and positive antinuclear antibodies, with anti-deoxyribonucleic acid antibodies of 33 U/mL (N < 30). In the extractable nuclear antigen (ENA) profile, the centromere B
protein was positive at 5.70 without any signs or symptoms of scleroderma. Complete blood count, renal function, electrolytes, and morning cortisol level were normal. The test result for antineutrophil cytoplasmic autoantibody (ANCA) was negative; the anti-Saccharomyces cerevisiae antibody (ASCA) and immunodeficiency profile was negative; and serological markers for tuberculosis, Epstein-Barr virus, hepatitis B and C, toxoplasmosis, syphilis, and human immunodeficiency virus were negative.

Computed tomography angiography of the lungs showed bilateral hilar and mediastinal adenopathy, numerous micronodules in the pulmonary parenchyma, and peribronchial thickening. Pulmonary embolism was excluded.

Pulmonary function tests showed a reduced diffusion capacity of carbon monoxide (DLCO) level (72% of the expected level), with preserved lung volumes and no obstruction. The patient’s echocardiogram was normal; her systolic pulmonary
artery pressure was 30 mm Hg. Bronchoscopy was normal. Bronchoalveolar lavage (BAL) fluid was sterile and contained 98% macrophages and 2% lymphocytes.

A bone scan showed a typical tracer pattern, with intense radiotracer uptake in the hilum and mediastinum and in posterior lung fields. There was also significant uptake in the soft tissue of both elbows and forearms (medially) and in that of the lower limbs (laterally), corresponding to the described subcutaneous nodules.

These subcutaneous skin nodules gradually resolved during her hospital stay, some seven weeks after her last dose of infliximab. Corticosteroid was not required, and she was discharged with close follow-up by her gastroenterologist. One month after discontinuation of infliximab, she was started on prednisone because of a flare-up of Crohn’s disease.

**Discussion and Literature Review**

Anti-TNF drugs are monoclonal antibodies that reduce the inflammatory response by interfering with the body’s production of TNF cytokines. These pharmaceutical molecules have dramatically changed the management of inflammatory diseases and are considered an efficient treatment option for rheumatoid arthritis, spondylarthritis, psoriasis, Crohn disease, and ulcerative colitis. Sarcoidosis is a granulomatous disease that can affect all organs. Although the etiology of sarcoidosis is still unknown, it is the interaction between CD4 T cells and specific antigen-presenting cells that results in the inflammation process and the formation of granulomas. The molecular mechanisms implicated in this process include the production of cytokines that activate lymphocytes and macrophages, with subsequent TNF production. This leads to the amplification of the inflammatory response and causes the formation of noncaseating epithelioid cell granulomas. Although the first-intention treatment of sarcoidosis remains prednisone, the use of the anti-TNF agent infliximab for treating prednisone-resistant sarcoidosis has had some reported success in a few small studies. The reports of patients developing sarcoid-like reactions during anti-TNF therapy are paradoxical and not yet understood. Most evidence of these adverse reactions comes from case reports. To date, 48 cases of anti-TNF–induced sarcoidosis have been reported; most were encountered in patients with inflammatory arthropathies (46/48) who were taking etanercept (28/48) or, less frequently, infliximab (14/48) or adalimumab (6/48). Molecular differences between these agents partly explain why more cases of sarcoidosis develop with etanercept than with the other two agents. Infliximab and adalimumab are TNF antibodies that suppress TNF better than etanercept does. Hence, the structural, pharmacokinetic, and pharmacodynamic differences between anti-TNF drugs correlate well with reports of more remissions of sarcoidosis when infliximab and adalimumab are used than when etanercept is used. Some studies even found a worsening of sarcoidosis during treatment with etanercept. In 2009, a well-designed French study with data taken from reports from members of a rheumatological association estimated the incidence of this reaction to be 1 in 2,800. One literature review (21 patients) noted that 85% of radiological patterns were stages I and II and that ACE values were high in 53% of patients. The same study noted that anti-TNF treatment was discontinued in all patients but that only 52% of patients were started on steroids.

For all patients who developed sarcoid-like reactions after starting an anti-TNF drug regimen, the discontinuation of the drug (with or without the use of corticosteroids) has led to improvement. When the causal agent was restarted, recurrence was observed. However, when a different anti-TNF agent was introduced, the outcome varied: some patients relapsed, and some did not.

To the best of our knowledge, this is the second case of infliximab–induced sarcoidosis in a patient with Crohn’s disease. More important, it is the first case of Löfgren syndrome developing during treatment with an anti-TNF drug.

**References**

Scrotal and Orbital Involvement in Extramedullary De-differentiated Multiple Myeloma

Gavin Docherty, Barret Rush, Gary Victor, Greg Dueck

Case Report

A 71-year-old Indian male presented with a five-month history of progressive bilateral testicular swelling and swelling of the left orbit or one month duration. Nine months ago, he had undergone four cycles of chemotherapy (bortezomib, cyclophosphamide, and dexamethasone) for an immunoglobulin A (IgA) lambda multiple myeloma (3.8 grams per decilitre [g/dL]). This was stage 3 according to the International Staging System (ISS) and had no adverse cytogenetics. The patient had undergone six more cycles of treatment prior to presentation. Physical examination revealed gross distension of the left orbital tissues with violaceous colouring (Figure 1A). The abdomen was distended with ascites. Genitourinary examination revealed testicular enlargement (Figure 1B). There was no erythema or warmth associated with either area. Laboratory tests failed to demonstrate monoclonal paraproteinemia, but his lactate dehydrogenase (LDH) level was elevated at 2068 units per litre (units/L). Abdominal paracentesis revealed a fluid cell count of 16,180 10⁶/L and a fluid LDH of 10,591 units/L. Cytology showed CD138 positivity, 80% for Ki-67, and lambda light chain restriction. These findings supported a diagnosis of de-differentiated extramedullary multiple myeloma. The prognosis and available management plans were discussed with the patient, and he was discharged to the community to be placed in the care of the palliative care team per his wishes.

Figure 1A. Left orbital involvement in extramedullary de-differentiated myeloma.

Figure 1B. Testicular involvement in extramedullary de-differentiated myeloma.
Discussion

Multiple myeloma is usually characterized by production of a monoclonal protein by neoplastic plasma cells. This case report describes a patient who was diagnosed with multiple myeloma and demonstrated an unconfirmed complete response to therapy. His disease then progressed in an atypical manner, with extraosseous involvement of the scrotum, abdomen, and left orbit and lack of progressive monoclonal protein. This case represents de-differentiation of the patient’s multiple myeloma, with subsequent escape from bone marrow and direct invasion of multiple tissues. The case was notable for loss of monoclonal protein in the serum, multiple extraosseous sites of involvement, and elevated LDH. Extramedullary tumour formation in multiple myeloma is a rare occurrence and rarely involves more than a single site. Varettoni et al. found that approximately 1% of patients presented with soft tissue or visceral disease. He also suggested that the incidence of extramedullary myeloma may be increasing. Associated features of de-differentiated myeloma include high-grade histology, loss of CD56 expression, resistance to therapeutic regimens, and association with a poor prognosis. De-differentiation and extramedullary involvement in multiple myeloma appears to be becoming more common. This may be caused by alteration of adhesion molecules, which allows plasmablasts to escape from bone marrow. Dawson et al. proposed that novel biological therapies may alter the microenvironment and introduce an evolutionary pressure that predisposes to the clonal formation of cells that have acquired stromal independence and lost the ability to secrete intact immunoglobulin. Additionally, Yaccoby suggested that a subpopulation of malignant cells may survive chemotherapy because of their proximity to osteoclasts. These cells may then emerge as aggressive clones at a later date. Their ability to do so is attributed to the plasticity inherent in multiple myeloma cells, which allows them to de-differentiate into an immature and resilient phenotype. Furthermore, it is important to consider the possibility that atypical presentations during relapse may not be the result of novel therapies but may represent the natural history of multiple myeloma in an era when patients are surviving longer as a result of current treatments.

Given the increasing incidence of de-differentiation and extramedullary involvement in multiple myeloma, it is important for clinicians to be aware of this mode of relapse.

Acknowledgments

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References

The Ethos of Medicine in Postmodern America:
Philosophical, Cultural and Social Considerations

Practising medicine in the silicon cage

Reviewed by Thomas Murray OCONS MD

We need good data to practise good medicine. However, if a system becomes
dominated by electronic health records (EHRs), computerized decision-making
programs, and excessive guidelines and protocols, physicians can become pawns in “the
silicon cage.”

Arnold Eiser, professor of medicine and associate dean at Drexel University College
of Medicine, is concerned about the erosion of both the patient-physician relationship
and professionalism in the corporate world of American medicine. This postmodern
world is characterized by what he calls “the three big C’s” of American medicine:
consumerism, computerization, and corporatization.

He notes that it is difficult to gain a broad perspective of the changes in health care
when you are living through it. To provide an overview, he employs a wide-angle lens
that includes postmodern philosophers, contemporary commentators, bioethicists, policy
makers, and experiences from other countries (although this final aspect is relatively thin).
Eiser begins by recounting the changes since 1970, when the health care system became
more corporate. This business model increasingly viewed health care as marketable
services and commodities, which was aided by challenges to the tradition of physician
power and paternalism, coupled with social trends that favoured individualism,
autonomy, and entitlements.

In the silicon cage, the myth of the physician hero has been replaced by the myth of
powerful computerized systems. Computers may be able to simulate a clinical hyper-
reality (e.g., when designing hospital care programs), but this does not mean they
prioritize the needs of the individual patient. For example, a patient can be logged into a
diagnostic category using a guideline-directed pattern of care that includes tests and
treatment. However, Eiser wonders how well a patient is served by these computerized
programs, particularly when the diagnosis changes or the patient has concomitant
diagnoses.

Eiser challenges us to question how much of the computerization of health care is
designed to enhance corporate control and profit margins. After all, corporations are
prevented from practising medicine, while physicians should be free to make independent
judgments. Corporate influence increases once we use computerized performance
measurements, guidelines, order sets, and protocols, and de-emphasizes individual
decision making by clinicians. He argues that unbridled enthusiasm for computerized
medicine is a perfect environment in which to increase bureaucratic control and erode professionalism; bureaucracies thrive on the centralization of information and power. The evidence for benefit to the individual patient is sparse, but computerized systems have become the prevailing cultural myth and are typically assumed to be superior. This approach is also driven by a corporate mindset toward efficiency and profit, agendas that are not always best for personal health care. Although the computerization of records has benefits, it changes the nature of the patient-physician relationship and reduces the individualization of patient care.

Eiser also persuades us to think about how much the information boom (including Internet and television advertising) serves patient autonomy and democratizes information, versus how much is just profit-driven marketing. It is probably both, but preserving the patient-doctor relationship in a marketplace system becomes more challenging. As Eiser notes, one problematic response has been the adoption by physicians of the business model.

He wisely asserts that we cannot just bemoan the loss of the old but, rather, must be inventive and perceptive with the new. Eiser suggests that a start would be to add a patient responsibility section to the list of patient rights, along with a section on physician rights and responsibilities. In addition, he recommends a list of duties and responsibilities for health executives.

How does one maintain humane medical practice in an era dramatically altered by consumerism, computerization, corporatization, direct-to-patient advertising and internet medical information? How does humanistic ethical medical practice survive in a corporate world that argues that a moral and ethical framework is unnecessary if market forces dominate?

Eiser states that recent enthusiasm for patient-centred care could be a reversal of the impersonal consumerism and corporatization of health care. However, he cautions that it could also be a smoke screen or a marketing ploy using the business concept of customer satisfaction for greater profit.

Measures of performance, quality improvement, and patient satisfaction can be positive. However, they can also mask other agendas. For example, the results look better when seriously ill or risky patients are de-insured from the system, or when the sickest people are dropped by physician panels and hospitals. This approach may be good business, but it violates the precepts of justice and beneficence. Financial incentives motivate performance for the good or for the bad; therefore, they can also undermine efforts geared toward clinical excellence and altruism. Pay-for-performance encourages the actions it measures but underemphasizes important aspects of care that are not measured. It puts at a disadvantage the physician who cares for the sickest, poorest, and least compliant patients.

The call for a re-evaluation of the role of physicians in this post-modern world of health care is no hollow cry. Physician burnout is increasing, and studies show that the leading causes are performing too many bureaucratic procedures, feeling like a cog in the medical industry, and the computerization of medical practice. Physicians in the 1990s began to talk about “the hassle factor.” Accordingly, a disturbing number of physicians would discourage their children, or any young person, from entering medicine.

My bookshelves sag with books that decry the losses of modern medicine, while a distressingly small number contain practical solutions. Eiser challenges us to think about how consumerism, the pursuit of profit, computerized protocols, Internet doctor ratings, blogs, and multiple stakeholders affect the patient-physician relationship. He is not so naive as to suggest we can roll back the cultural revolution that is under way, and he questions whether the humanistic era really ever existed. However, he does strive to preserve a meaningful individualized patient-physician relationship amidst rapid change. Realizing that corporate forces are hard to reverse, he calls for a “not-so-profitable healthcare organization that embraces an ethical value in addition to profitability.”

The Ethos of Medicine in Postmodern America is a thoughtful, informative book by an experienced clinician, educator, and ethicist. It introduces a broad view of a complex system about which we may previously have had simplistic opinions. This is primarily an American story, but similar changes are afoot in Canada and elsewhere.
Clinical use:

Xarelto® is not recommended for use in children less than 18 years of age.

Contraindications:

- Clinically significant active bleeding, including gastrointestinal bleeding
- Lesions or conditions at increased risk of clinically significant bleeding, e.g., recent cerebral infarction (hemorrhagic or ischemic), active peptic ulcer disease with recent bleeding, patients with spontaneous or acquired impairment of hemostasis
- Concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-glycoprotein (P-gp), such as ketoconazole, itraconazole, posaconazole, or ritonavir
- Concomitant treatment with any other anticoagulant, including:
  - unfractionated heparin (UFH), except at doses used to maintain a patent central venous or arterial catheter,
  - low molecular weight heparins (LMWH), such as enoxaparin and dalteparin,
  - heparin derivatives, such as fondaparinux, and
  - oral anticoagulants, such as warfarin, dabigatran, apixaban, except under circumstances of switching therapy to or from Xarelto®.
- Hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy, and having clinically relevant bleeding risk
- Pregnancy
- Nursing women
- Hypersensitivity to Xarelto® (rivaroxaban) or to any ingredient in the formulation

Most serious warnings and precautions:

PREMATURE DISCONTINUATION OF ANY ORAL ANTICOAGULANT, INCLUDING XARELTO®, INCREASES THE RISK OF THROMBOTIC EVENTS. To reduce this risk, consider coverage with another anticoagulant if Xarelto® is discontinued for a reason other than pathological bleeding or completion of a course of therapy.

Bleeding: Xarelto® (rivaroxaban), like other anticoagulants, should be used with caution in patients with an increased bleeding risk. Any unexplained fall in hemoglobin or blood pressure should lead to a search for a bleeding site. Patients at high risk of bleeding should not be prescribed Xarelto®. Should severe bleeding occur, treatment with Xarelto® must be discontinued and the source of bleeding investigated promptly. See Relevant warnings and precautions for concomitant use of drugs affecting hemostasis.

Peri-operative spinal/epidural anesthesia, lumbar puncture: The risk of developing an epidural or spinal hematoma that may result in long-term neurological injury or permanent paralysis is increased by the use of indwelling epidural catheters or the concomitant use of drugs affecting hemostasis. Accordingly, the use of Xarelto®, at doses greater than 10 mg, is not recommended in patients undergoing anesthesia with post-operative indwelling epidural catheters. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, the administration of Xarelto® should be delayed for 24 hours. Patients who have undergone epidural puncture and who are receiving Xarelto® should be frequently monitored for signs and symptoms of neurological impairment. The physician should consider the potential benefit versus the risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis and use Xarelto® only when the benefits clearly outweigh the possible risks. An epidural catheter should not be withdrawn earlier than 18 hours after the last administration of Xarelto®, Xarelto® should be administered not earlier than 6 hours after the removal of the catheter.

Renal impairment: Xarelto® is not recommended in patients with severe renal impairment. Xarelto® should be used with caution in patients with moderate renal impairment (CrCl 30-49 mL/min), especially in those concomitantly receiving other drugs which increase rivaroxaban plasma concentrations. Determine estimated creatinine clearance (eCrCl) in all patients before instituting Xarelto®.

Monitoring and laboratory tests: Although Xarelto® therapy will lead to an elevated INR, depending on the timing of the measurement, the INR is not a valid measure to assess the anticoagulant activity of Xarelto®. The INR is only calibrated and validated for vitamin K antagonists (VKA) and should not be used for any other anticoagulant, including Xarelto®.

Other relevant warnings and precautions:

- Fall in hemoglobin or blood pressure
- Concomitant use of drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), and platelet aggregation inhibitors
- Atrial fibrillation and having a condition that warrants single or dual antiplatelet therapy
- Use of antiplatelet agents, prasugrel and ticagrelor
- Use of thrombolytics during acute myocardial infarction (AMI) or acute stroke due to expected increased risk of major bleeding
- Patients with prosthetic heart valves or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis
- Interaction with moderate CYP 3A4 inhibitors
- Interaction with strong CYP 3A4 inducers, such as rifampicin, and the anticonvulsants, phenytoin, carbamazepine, phenobarbital
- Patients with hepatic impairment
- Patients who undergo surgery or invasive procedures including pre-operative phase (associated with risk of bleeding) and peri-operative phase when neuraxial (epidural/spinal) anesthesia or spinal puncture is performed (associated with risk of epidural or spinal hematoma that may result in long-term neurological injury or permanent paralysis) and post-procedural period (to avoid unnecessary increased risk of thrombosis
- Patients with lactose sensitivity

For more information:

Please consult the Xarelto® Product Monograph at http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece. The product monograph is also available by calling 1-800-265-7382.

Xarelto® is indicated for:
- prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate.
- treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE.
- prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR) surgery.

For the treatment of VTE, Xarelto® is not recommended as an alternative to unfractionated heparin in patients with acute pulmonary embolus who are hemodynamically unstable, or who may receive thrombolysis or pulmonary embolectomy, since the safety and efficacy of Xarelto® have not been established in these clinical situations.

Extensive experience with Xarelto®
- More than 8 million patients treated in clinical practice worldwide across all indications
- #1 dispensed NOAC† by Hematologists, Internists and Orthopaedic Surgeons
- An extensive clinical program is investigating Xarelto® in over 55 currently active clinical trials worldwide

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Simple Once-Daily* Dosing in All Vascular Indications

Refer to the page in the bottom right icon for additional safety information and for a web link to the Xarelto® Product Monograph discussing:
- Contraindications: clinically significant active bleeding including gastrointestinal bleeding; lesions or conditions at increased risk of clinically significant bleeding, e.g., recent cerebral infarction (hemorrhagic or ischemic), active peptic ulcer disease with recent bleeding, patients with spontaneous or acquired impairment of hemostasis; concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-glycoprotein (P-gp); concomitant treatment with any other anticoagulant (including unfractionated heparin [UFH]) except at doses used to maintain a patent central venous or arterial catheter; low molecular weight heparins [LMWH]; heparin derivatives; and oral anticoagulants except under circumstances of switching therapy to or from Xarelto®; hepatic disease associated with coagulopathy and having clinically relevant bleeding risk; pregnancy; nursing women; hypersensitivity to Xarelto® (rivaroxaban) or to any ingredient in the formulation.
- Most serious warnings and precautions regarding: premature discontinuation of any anticoagulant; high risk of bleeding; peri-operative spinal/epidural anesthesia and lumbar puncture; moderate or severe renal impairment; and use of the INR to measure the anticoagulant activity of Xarelto®.
- Other relevant warnings and precautions regarding: fall in hemoglobin or blood pressure, concomitant use of drugs affecting hemostasis, atrial fibrillation and having a condition that warrants single or dual antiplatelet therapy, use of antiplatelet agents, prasugrel and ticagrelor, use of thrombolytics during acute myocardial infarction (AMI) or acute stroke (due to expected increased risk of major bleeding), patients with prosthetic heart valves or those with hemodynamically significant rheumatic heart disease, interaction with moderate CYP 3A4 inhibitors and strong CYP 3A4 inducers, patients with hepatic impairment, patients undergoing surgery or invasive procedures, patients with lactose sensitivity.
- Conditions of clinical use, adverse reactions, drug interactions and dosing instructions.

The product monograph is also available by calling 1-800-265-7382.

†NOAC: Newer Oral Anticoagulant. NOACs are comprised of the following products: Xarelto®, Eliquis and Pradaxa.